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Oral and Dental Phenotype of Dyskeratosis Congenita

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Abstract

Dyskeratosis congenita (DC) is an inherited bone marrow failure syndrome that is characterized by lacey reticular hyperpigmentation of the skin, dystrophic nails, mucous membrane leukoplakia and pancytopenia. Diagnosis may be delayed until clinical signs are apparent. Severe pancytopenia frequently causes early mortality of DC patients, who have an increased risk of developing oropharyngeal squamous cell carcinoma. Several case reports have described oral changes in DC, which include oral leukoplakia, increased dental caries, hypodontia, thin enamel structure, aggressive periodontitis, intraoral brown pigmentation, tooth loss, taurodontism and blunted roots. We determined the prevalence of these previously reported findings in a cohort of 17 patients with DC and 23 family members. The most common oral changes in DC patients were oral leukoplakia (65% of the entire DC population), decreased root/crown ratio (75% with sufficient tooth development) and mild taurodontism (57% with sufficient tooth development). From the clinical perspective, a diagnosis of DC or other inherited bone marrow failure syndrome should be considered in young persons with oral leukoplakia, particularly those with no history of smoking. Multiple permanent teeth with decreased root/crown ratios further suggest DC.

Keywords

dyskeratosis congenita; leukoplakia; tooth development; *DKC1*; *TERC*; *TERT*

Introduction

Early in the 1900s, Zinsser, Cole and Engman described an inherited variant of ectodermal dysplasia that affected skin, nails and mucous membranes¹. The syndrome eventually became known as dyskeratosis congenita (DC), and is classified as one of the Inherited Bone Marrow Failure Syndromes (IBMFS). Classic DC is characterized by dystrophic nails, reticular lacey hyperpigmentation of the skin, and mucous membrane leukoplakia². Further studies have established DC as a multi-system disorder in which affected patients often develop single or pancytopenia, abnormalities of the eye, lacrimal duct stenosis, pulmonary fibrosis and malignancy, in addition to changes of skin and mucosa³. Although onset may occur in early childhood, diagnosis is often delayed until clinical signs are apparent. Early mortality of DC patients is frequently due to severe pancytopenia. More than 275 unique patients with DC have been reported from all major ethnic groups².

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The presumed underlying defect in DC is an inability to preserve telomere length secondary to mutations in the genes for RNA or proteins composing this ribonucleoprotein complex³. Chromosome ends are capped by telomeres, which are protective DNA-protein complexes. Telomeres shorten progressively with successive cell divisions in most cells, and cell division ceases when telomere length becomes critically short. Germ cells and selected stem cells must have a mechanism to preserve telomere length to continue cell division and provide new cells for many tissues³. In healthy cells, a ribonucleoprotein reverse transcriptase complex, telomerase, maintains telomere length by protecting telomeric end caps of chromosomes. To date, mutations of genes encoding the RNA template (*TERC*), telomerase catalytic reverse transcriptase (*TERT*) and dyskerin, a component of the telomerase complex, have been identified in various DC families^{4, 5}. Clinically there appear to be three patterns of inheritance for DC: autosomal dominant (AD), autosomal recessive (AR) and X-linked recessive (XLR)². Mutations of the gene *DKC1* (located at Xq28), which encodes nucleolar protein dyskerin, are found in XLR DC, whereas mutations in *TERC* and *TERT* have been identified in some AD DC families. No mutations have been identified in more than half the known patients in large series, and thus additional DC genes await identification².

Tissues with cell populations that must regenerate frequently are most affected in DC. The most serious complications are greatly increased risks of bone marrow failure, cancer at an early age, infection, and hemorrhage². A literature review found 45 cases of early cancers reported out of an estimated 274 patients, and most cancers were squamous cell carcinoma (SCC)². The oropharynx was the site of 17 of these reported SCC, assumed to arise from the chronic mucosal leukoplakia that develops at a very young age in many of these patients². In addition to their increased risk of cancer, DC patients have a significant burden of disease, as they may become transfusion-dependent and require repeated hospitalizations for infections⁶. These increased susceptibilities to multiple complications necessitate early diagnosis to institute treatments such as hematopoietic stem cell transplant, androgens, or hematopoietic growth factors.

IBMFS are diagnosed by physical and laboratory findings, often in conjunction with evidence of familial segregation apparent from the family pedigree. Many times genetic testing will not identify a specific mutation². Several case reports have described specific oral changes in association with DC. These include oral leukoplakia, increased dental caries, hypodontia, thin enamel structure, aggressive periodontitis, intraoral brown pigmentation, tooth loss, taurodontism and blunted roots^{7–10}. To establish the phenotypes of various IBMFS, including DC, the Clinical Genetics Branch of the National Cancer Institute (NCI) is extensively evaluating patients and family members with these disorders. A thorough oral examination is part of the evaluation. This report presents the oral and dental findings of 17 patients with DC and 23 family members.

Methods and Materials

Study design

This was a cross-sectional study of patients with an IBMFS and their family members. All consented to a protocol approved by the NCI Institutional Review Board. This study includes evaluations conducted between January 2003 and March 2006. The majority of patients were evaluated only once.

Subjects

Seventeen patients with DC and 23 family members, representing twelve different families, were evaluated. In nine families, the members affected with DC were examined. Three

families were evaluated after the affected member had died. No patients had known consanguineous parentage. Fourteen healthy IBMFS family members (< 31 years of age) and one additional healthy male served as an age and sex appropriate control group for studies of dental indices (Decayed, Missing and Filled permanent Surfaces or DMFS) and root development. These controls were relatives of patients with Fanconi Anemia, Diamond-Blackfan Anemia and Shwachman-Diamond Syndrome.

Examination

A standardized, detailed health history, including smoking history, was collected at the time of the physical examination. Concurrent laboratory studies were performed at the National Institutes of Health Clinical Center. Every patient had a comprehensive oral examination, including radiographs in 16/17. Panoraphic radiographs were evaluated from twelve DC patients, a panel of 6 intraoral radiographs (4 periapical and 2 bite-wing exposures) from four DC patients, while one 3 year old patient was too young to obtain diagnostic radiographs. Clinical and radiographic evidence of caries and existing restorations were recorded. The location and type of soft tissue lesions were noted and photographed. The World Health Organization (WHO) definition of oral leukoplakia ("a white patch or plaque that cannot be characterised, clinically or pathologically as any other disease") was used to classify white lesions¹¹. Root lengths and crown lengths of all permanent first and second molars and premolars with radiographically closed apices were calculated from panoraphic radiographs¹². Evidence of past or present aggressive periodontitis (>50% generalized alveolar bone loss) was determined radiographically for 12 patients. Taurodontism was calculated from radiographs using the method described by Shifman and colleagues¹³ that involves determining the distance between the lowest point of the roof of the pulp chamber to the apex of the longest root, and distance between the baseline connecting the two CEJ and the highest point in the floor of the pulp chamber. Three degrees of taurodontism can be calculated from this index (hypotaurodontism or mild, mesotaurodontism or moderate and hypertaurodontism or severe).

Mutational analyses

Mutations in *DKC1*, *TERC*, and *TERT* were identified by bi-directional sequencing of PCR-amplified fragments (GeneDx, Inc., Gaithersburg, MD).

Statistical methods

DMFS scores and the percentage of posterior teeth with decreased root/crown ratios of the control and DC groups were compared using Student's t-test. Frequencies of leukoplakia, brown pigmentation, decreased root/crown ratios, taurodontism, thin enamel, hypodontia, and aggressive periodontitis in the control and DC groups were compared with Fisher's exact test. The $p < 0.05$ value was used for significance.

Results

Patient and family characteristics

The 17 patients with DC represented nine different families. Mutational analyses established the distinct mutation in nine patients, of whom five had mutant *DKC1*, three had mutant *TERC* and one had mutant *TERT* (Table 1). The other eight did not have mutations in those genes, and were diagnosed by clinical findings and pedigree. Thirteen patients were male and four were female, ranging in age from 3 to 46 years (mean $\pm$ 1 standard deviation (SD) = 18.1 ± 10.5 years, median 15 years), with 16 of 17 patients under the age of 30 years. Fifteen of the 17 had anemia, neutropenia, and/or thrombocytopenia when evaluated at the clinic (Table 1). Three patients required regular transfusions of red blood cells and platelets.

Three were treated with androgens (only one was responding), one was receiving both granulocyte colony stimulating factor and erythropoietin, and one was receiving granulocyte colony stimulating factor.

A total of 23 clinically unaffected family members were evaluated, including six individuals from three families in which the proband was deceased. The family group consisted of 14 females and 9 males, ranging in age from 7 years to 63 years (mean $\pm$ 1 SD = 37.9 years $\pm$ 14.8 years; median 36 years, Table 2). The sex ratio in the family members was not significantly different than in the patients, but the family members were significantly older ($p < 0.001$). Four females were heterozygous for mutant *DKC1*, and six (three males and three females) did not have the mutated gene in families with known mutations. Carrier status of the other 13 family members was unknown, or presumed normal from the pedigree.

Soft tissue lesions

Intraoral soft tissue changes were found in 12 of 17 DC patients (Table 3). Findings were classified by appearance and by location into the following categories: leukoplakia (excluding prominent linea alba), erythema, brown pigmentation, and papillary atrophy on the tongue. Oral leukoplakia, present in 11 DC cases, was the most frequently found oral change in this group, with the most common sites being the tongue ($n = 9$, Table 3, Figure 1), buccal mucosa ($n=5$), palate ($n=2$) and gingiva ($n=1$). The leukoplakia of the tongue varied in presentation. It was found in isolated patches (Figure 1A), as a fine reticular pattern (1B) or as a plaque-like leukoplakia distributed across the entire tongue dorsum (Figure 1C and 1D). In three younger patients (ages 9, 10 and 13 years), leukoplakia accompanied papillary atrophy of the tongue (Figure 1A, 1B). We could not find an age-related pattern or genotype/phenotype correlation in the varied clinical patterns of leukoplakia. Patients with either *TERC* or *DKC1* mutations presented with leukoplakia on the tongue and/or buccal mucosa. The one patient with a known mutation of *TERT* did not have leukoplakia. Only three of the eleven patients with leukoplakia had a history of any tobacco use, defined as >100 cigarettes smoked in a lifetime or use of any other tobacco product.

Erythema, the second most common soft tissue finding in DC patients, was found in eight patients with or without thrombocytopenia. These erythematous areas on either the buccal mucosa or tongue appeared to be sites that had lost the superficial epithelium without disruption of the underlying connective tissue (Figure 1A, Figure 2). The erythematous patches on the buccal mucosa were at the level of the occlusal plane (Figure 2), suggesting the surface tissue sloughed after contact with the teeth. These areas were only present in patients who also had oral leukoplakia. Five patients had petechiae of the buccal mucosa, and one patient with significant thrombocytopenia had a hematoma on the lip.

The last distinct soft tissue change found in the DC patient group was brown pigmentation of the tongue (Figure 1D), which was present in only two patients. These individuals, an African-American female and a Caucasian male, both had mutations in *TERC*.

Biopsies of the oral lesions were not obtained from patients enrolled in this study as most had very low platelet counts and were followed by other practitioners in their home communities.

No notable soft tissue changes were identified in family members.

Periodontal changes

No patient had radiographic evidence of past or present aggressive periodontitis.

Tooth changes

Since previous studies reported increased caries in DC, DMFS scores of 15 DC patients between the ages of 6 and 29 years (mean $\pm$ 1 SD = 17.2 years $\pm$ 7.3 years; median 15 years) were compared with sex and aged matched IBMFS family controls (age range 7 to 31 years, mean $\pm$ 1 SD = 16.1 years $\pm$ 7.4 years; median 14 years). There was no significant difference ($p > 0.05$) in the number of decayed surfaces, missing teeth, filled surfaces or overall DMFS scores (data not shown). There was no evidence of thin enamel in the 16 DC patients with radiographs. Hypodontia (consisting only of congenitally missing premolars) was noted in two patients with DC and one control.

The difference between the proportion of teeth with decreased root/crown ratios was compared for the DC group and the family member control group and found to be significantly different ($p < 0.007$, Fisher's exact test). This finding was the most pronounced hard tissue change in DC (Tables 4 and 5) and was visible on panoramic radiographs from several patients (Figures 3 and 4). This decreased ratio was secondary to decreased root length, as the heights of the crowns were not significantly different between the two groups (data not shown). The decreased root/crown ratio was found in at least four posterior teeth in 6 of 8 DC patients with sufficient radiographs and tooth development for evaluation (at least 13 years of age), and appeared to be developing in three children ages 9 or 10 years old (data not shown). Only one DC family member had multiple teeth with decreased root/crown ratios. This female who had one copy of mutant *DKC1* (and three male children with DC) had eight teeth with decreased ratios. Shortened incisor roots were visible in a few panoramic radiographs from DC patients, but these teeth were excluded from analysis as anterior teeth are often indistinct in this type of radiographic image. Since this was a cross-sectional rather than longitudinal study, it was not possible to determine whether the rate of root growth was also retarded in DC. Shortened roots were observed in individuals with mutations of the *TERT*, *DKC1* or *TERC* genes. Taurodontism of the mildest Shifman class was noted in four of seven patients (Figures 3 and 4, Table 5) and none of the controls. Statistical analyses (two-sided Fisher's exact test) confirmed that oral leukoplakia ($p < 0.001$), decreased root/crown ratios of the posterior teeth ($p = 0.007$) and taurodontism ($p = 0.015$) occurred more frequently in the DC group (Table 5).

Discussion

Controlled studies of the associated oral and dental findings in DC have not been reported previously. Although the prevalence of oral leukoplakia has been reported in larger cohorts, other previously reported dental findings were identified from case reports of one or two patients. In this study of 17 individuals with DC, the most commonly found oral changes were oral leukoplakia (65% of the entire population), decreased root/crown ratio (75% of patients with sufficient tooth development to permit evaluation) and mild taurodontism (57% with radiographs and sufficient tooth development to permit evaluation). Other previously reported oral features of this disease, increased dental caries, hypodontia, thin enamel and aggressive periodontitis, were not detected in this DC population.

The most common change of the oral mucosal tissues in DC was leukoplakia, one of the three features originally described in this disease. It was not present in every patient, and the prevalence in our cohort (65%) is similar to the 78% prevalence reported from a registry of 118 male patients with presumed XLR DC¹⁴. The clinical presentation of oral leukoplakia in these patients was very heterogeneous, which is consistent with the clinical variability reported for the skin changes associated with DC¹⁴. Other authors have proposed that the heterogeneity of the clinical DC presentation suggests modification of the phenotype by other genetic factors and/or the environment.

Very little is known about the histopathological features of oral leukoplakia in DC. A longitudinal study of one patient characterized histological features associated with progression from hyperkeratosis to dysplasia of a lesion on the tongue¹⁵. The dysplastic tissue from the ventral tongue exhibited abnormal keratin expression, consisting of co-expression of keratins K16, K10 and K13¹⁵. p53 expression was not found in the first biopsy, but was present in all subsequent specimens. Unfortunately, no biopsies of leukoplakic tissues were available to permit similar studies from our patients.

In addition to leukoplakia, the tongues in some patients demonstrated atrophy of the papilla. The mechanism underlying this atrophy may be provided by studies with a mouse model (mTR+/- mice on the CAST/EiJ) of autosomal dominant DC¹⁶. Interbreeding of these mice that are heterozygous for deficiency of the RNA subunit of telomerase creates progressive telomere shortening. Histopathological examination of the intestines of later generation mice found crypt depletion and villi atrophy, suggesting normal telomere length is needed for maintenance of these tissues¹⁶. It is possible there is a similar requirement to maintain adequate telomere length to sustain healthy tongue epithelium, which is in constant need of replenishment from basal cells¹⁷.

Intraoral brown pigmentation, found in two patients with *TERC* mutations, may reflect an imbalance in telomerase activity. Recent work has demonstrated chromosomal imbalances involving *TERC* and *TERT* in various types of malignant melanoma¹⁸.

The finding of shortened roots in a high percentage of DC patients suggests normal telomere length or adequate telomerase activity is needed for complete root development. Two other reports further support this hypothesis. A recent study found cementoblast progenitor cells, believed to be responsible for root development, were immortalized by expression of human telomerase reverse transcriptase (*TERT*) and the gene for polycomb group protein, *Bmi-1*¹⁹. Transduced single cell clones subsequently expressed mRNA for bone sialoprotein, osteocalcin, osteopontin, and type I collagen when implanted in immunodeficient mice. In another report, stem cells, which require functional telomerase, were identified in the apical root during certain stages of root formation of the rat tooth²⁰. Alternatively, it is possible that the proteins encoded by the mutated genes in DC have functions in root and oral epithelial development by mechanisms not yet defined.

Root development of teeth may also provide information about the time of disease progression in patients with DC. Root development begins after the crown of the tooth is formed. The earliest root development of the permanent teeth occurs at about age 3 years, beginning with the central incisors²¹⁻²³. The second permanent molar roots begin to form between age 7 and 8 years. Insults to the developing teeth, such as radiation, chemotherapy and/or hematopoietic stem cell transplant during that time can disturb root development²². Children surviving cancer may present later in life with clinically normal crowns and abnormally short roots of certain teeth²², marking the time of their cancer therapy. It is likely that a portion of dental follicular cells responsible for root development in DC cease functioning as telomeres shorten through repeated divisions. If all of the roots of the permanent teeth in a DC patient are short, telomerase activity or telomere length may have been inadequate since early childhood. If the only teeth with short roots are the second permanent molars, then telomerase activity may have been adequate until the early teenage years.

Taurodont teeth have enlarged pulp chambers and short roots¹³. Since root length is reduced in the DC patients, it was not surprising that taurodontism was found in four of seven evaluated patients. In addition, pulp chambers normally decrease in size with age because of secondary dentin deposition²⁴. This process is believed to be mediated by stem cells in

dental pulps that express dentin sialoprotein (DSP)²⁵. It is possible that pulp stem cells that produce secondary dentin also are dysfunctional in DC. However, this presumed dysfunction did not appear to be profound, as the taurodontism in our patients was of the mildest form using the classification system of Shifman¹³.

Previously reported oral findings (aggressive periodontal disease, increased dental caries, thin enamel and hypodontia) associated with DC were not part of the oral phenotype found in this cohort. We were surprised that none of our patients had evidence of past or current aggressive periodontitis, and feel this may reflect the better dental hygiene of these DC patients or their absence of profound neutropenia. Most had absolute neutrophil counts (ANC) >1000 cells/ μ L (Table 1). One of the patients with an ANC <1000 cells/ μ L had radiographic suggestions of alveolar bone loss in the posterior teeth, but she was also undergoing full orthodontic therapy. Therefore, alveolar bone height assessments using radiographs were considered unreliable. Dental radiographs were not obtainable on the 3 year old with decreased ANC. Other previously reported findings of increased caries, hypodontia and thin enamel^{7, 9, 26} were not confirmed in this study. Given the heterogeneous nature of this patient group, these findings might be found in a larger study of patients and appropriate controls. In particular, studies of dental caries must be of significant size to control for the multiple other factors associated with caries in children^{27, 28} to determine whether the frequency of caries is increased in DC.

In summary, the oral phenotype of DC is characterized by leukoplakia, decreased root/crown ratios and mild taurodontism. From the clinical perspective, a diagnosis of DC or another inherited bone marrow failure syndrome should be considered in any young person with oral leukoplakia, particularly those with no history of tobacco use. Continued studies with this cohort should define the oral phenotype more completely and determine what factors are most associated with the development of oral squamous cell carcinomas in these patients.

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Figure 1. Varied presentation of leukoplakia in patients with dyskeratosis congenita

1A: Erythema, leukoplakia and papillary atrophy of the tongue in a 9 year old female, mutant gene unknown.

1B: Mild Papillary atrophy and leukoplakia of the tongue in a reticular pattern in a 10 year old male with mutant *DKC1*.

1C: Plaque-like leukoplakia on the dorsum of the tongue in a 21 yr old male, mutant gene unknown.

1D: Plaque-like leukoplakia with brown pigmentation of tongue in a patient with mutant *TERC*.

Figure 2. Erythema and diffuse leukoplakia of the buccal mucosa in a 10 year old male with mutant *DKC1*.

Figure 3.
Panorex radiograph from a 13-year-old male with mutant *DKC1* showing decreased root/crown ratios in the posterior teeth and taurodontism

Figure 4. Radiograph from a 25-yr-old with mutant *TERT* and generalized decreased root/crown ratios in the posterior teeth.

Table 1

Features of DC patients*

Family Number	Case Number	Age on exam, yrs	Sex	WBC** (K/ μ L)	ANC** (K/ μ L)	Hb** (g/dL)	MCV**	Platelet Count (K/ μ L)	Inheritance Pattern	Mutant gene	Treatment
1	1	46	F	5.150	2.735	12.8	115	28	AD**	<i>TERC</i> **	Halotestin
1	2	15	M	4.440	2.202	14.7	101	99	AD	<i>TERC</i>	
2	3	25	M	3.550	1.945	10.7	113	77	AD	<i>TERT</i> **	
3	4	26	F	2.460	1.707	8.1	110	64	AD	unknown	Oxymetholone
3	5	25	M	3.460	1.817	14.6	96	148	AD	unknown	
3	6	13	M	3.290	1.415	13.9	89	188	AD	unknown	
3	7	29	M	4.340	2.209	15.1	96	142	AD	unknown	
3	8	22	M	3.790	1.766	14.5	99	117	AD	unknown	
3	9	21	M	3.130	1.681	12.1	109	24	AD	unknown	
4	10	10	M	3.570	1.571	9.6	106	25	XLR**	<i>DKC1</i> **	
5	11	22	M	2.740	1.403	10.0	118	24	XLR	<i>DKC1</i>	
6	12	9	M	2.400	0.71	10.7	103	14	XLR	<i>DKC1</i>	G-CSF**, Aranesp, RBC** and platelet transfusions
6	13	3	M	2.160	0.616	9.5	98	16	XLR	<i>DKC1</i>	
6	14	13	M	3.600	1.897	12.9	97	45	XLR	<i>DKC1</i>	
7	15	15	F	2.180	0.392	7.9	114	17	AD	<i>TERC</i>	
8	16	9	F	2.620	1.022	9.5	87	12	unknown	unknown	G-CSF, RBC and platelet transfusions
9	17	6	M	3.380	1.213	9.1	112	110	unknown	unknown	Oxymetholone, prednisone, RBC and platelet transfusions

* Shaded values are outside the reference range.

WBC = white blood cells, ANC = absolute neutrophil count, Hb = hemoglobin, MCV = mean corpuscular volume, AD = autosomal dominant, *TERC* = gene encoding the RNA component of telomerase^{2, 4, 5}, *TERT* = gene encoding human telomerase reverse transcriptase³, XLR = X-linked recessive, *DKC1* = gene encoding the dyskerin protein³, G-CSF = granulocyte colony stimulating factor, RBC = red blood cells

Table 2

Features of DC family members

Family Number	Age on exam (yrs)	Sex	Inheritance	Carrier Status
3	30	Female	AD	Unknown
3	33	Male	AD	Unknown
3	28	Male	AD	Unknown
3	51	Female	AD	Presumed normal
4	13	Male	XLR	Unknown
4	36	Male	XLR	Unknown
4	41	Female	XLR	Unknown
5	34	Female	XLR	Normal
5	25	Female	XLR	Normal
5	50	Male	XLR	Normal
5	54	Female	XLR	Heterozygous for mutant <i>DKC1</i>
6	36	Male	XLR	Normal
6	36	Female	XLR	Heterozygous for mutant <i>DKC1</i>
7	48	Female	AD	Normal
8	48	Male	AD	Unknown
8	42	Female	AD	Unknown
8	7	Female	AD	Unknown
10	29	Female	XLR	Heterozygous for mutant <i>DKC1</i>
10	61	Male	XLR	Normal
10	58	Female	XLR	Heterozygous for mutant <i>DKC1</i>
11	63	Female	Unknown	Unknown
12	24	Female	Unknown	Unknown
12	24	Male	Unknown	Unknown

DC, dyskeratosis congenital; AD, autosomal dominant

Table 3

Abnormal soft tissue findings

Case number	Age on exam, yrs	Findings	Tongue	Buccal mucosa	Gingiva	Palate	Floor of mouth	Smoking history*	Mutant Gene
2	15	Brown pigmentation	XX					no	<i>TERC</i>
4	26	Leukoplakia			XX			yes	unknown
		Erythema	XX						
7	29	Plaque-like leukoplakia	XX					no	unknown
		Erythema		XX					
8	22	Leukoplakia		XX		XX		yes	unknown
9	21	Plaque-like leukoplakia	XX	XX		XX		no	unknown
10	10	Leukoplakia	XX	XX				no	<i>DKC1</i>
		Erythema with mild papillary atrophy	XX	XX					
11	22	Plaque-like leukoplakia	XX	XX			XX	yes	<i>DKC1</i>
		Erythema	XX	XX			XX		
12	9	Reticular leukoplakia	XX					no	<i>DKC1</i>
		Erythema		XX					
13	3	Plaque-like leukoplakia	XX					no	<i>DKC1</i>
		Erythema		XX					
14	13	Leukoplakia	XX					no	<i>DKC1</i>
		Erythema with papillary atrophy	XX		XX				
15	15	Plaque-like leukoplakia	XX	XX				no	<i>TERC</i>
		Brown pigmentation	XX	XX					
16	9	Leukoplakia	XX					no	Unknown
		Erythema with papillary atrophy	XX						

* Smoking = >100 cigarettes in life or use of any other type of tobacco product

Table 4

Root/crown ratio of posterior teeth, DC patients and IBMFS family controls

Controls			DC patients	
Sex	Age	Number of teeth below published norms*	Age	Number of teeth below published norms*
Female	41	1/16	46	2/15
Male	14	1/16	15	0/16
Male	31	1/15	25	9/16
Male	29	2/16	29	6/9
Male	21	0/14	22	5/16
Male	16	0/16	19	9/16
Male	24	0/16	22	16/16
Male	13	2/16	13	4/4 **

DC, dyskeratosis congenita

* Abnormal = Less than normal mean – 2 s.d. The difference between the proportion of teeth with decreased root/crown ratios in the DC group and control group is significant, $P < 0.003$ (unpaired t test). Not all posterior teeth could be evaluated.

** Other posterior teeth had orthodontic brackets.

Table 5

Frequency of oral hard and soft tissue abnormalities in DC patients and family members

<i>Finding</i>	<i>Controls</i>		<i>DC Patients</i>		<i>P value</i> [*]
	Yes	No	Yes	No	
Leukoplakia	1	22	11	6	P < 0.001
Erythema	2	21	8	9	P < 0.01
Brown pigmentation	0	23	2	15	NS
Papillary atrophy	0	23	3	14	NS
Decreased root/crown ratio in at least 4 posterior teeth ^{**}	0	8	6	2	P = 0.007
Taurodontism ^{**}	0	10	4	3	P = 0.015
Thin enamel ^{**}	0	16	0	16	NS
Hypodontia	1	15	2	14	NS
Aggressive periodontitis	0	23	0	16	NS

DC, dyskeratosis congenital; NS, not significant

^{*} The frequencies of the findings in the DC group and the family member control group were compared using Fisher's exact test. DC family members were used as controls for all comparisons except decreased root/crown ratio. Eight age and sex matched healthy IBMFS family members were used as controls for this comparison.

^{**} Not all DC patients had evaluable radiographs, or were too young to determine if root formation was abnormal or taurodontism was present.