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Availability Of Dental Anomaly Phenotype In Individuals With Familial Adenomatous Polyposis

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AVAILABILITY OF DENTAL ANOMALY PHENOTYPE IN INDIVIDUALS WITH FAMILIAL ADENOMATOUS POLYPOSIS

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TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

LIST OF TABLES

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Background: Mutations in the *APC* gene cause familial adenomatous polyposis (FAP), an autosomal dominant colorectal cancer predisposition associated with the development of hundreds to thousands of adenomatous colorectal polyps beginning in childhood or adolescence. Both malignant and non-malignant extracolonic manifestations are associated with *APC* gene mutations, including approximately 17% of individuals with various dental anomalies. The availability of dental anomaly information in the medical record remains to be evaluated.

Methods: Medical records were reviewed for documentation of dental anomalies. Dental questionnaires were mailed to 271 individuals with FAP at The University of Texas M. D. Anderson Cancer Center (UTMDACC) to assess self-reported dental phenotype. Demographic data was obtained from chart review and included current age or age at death, age at diagnosis of FAP, sex, surgical procedure for polyposis, available dental phenotype information, date of last contact at UTMDACC, and *APC* gene mutation and codon.

Results: The response rate to the dental questionnaire was 21%. The majority of individuals (82%) were did not have dental anomaly information available in the medical record. Forty-four (16%) had self-reported dental anomalies in either the medical record or on the dental questionnaire. The most frequently reported anomalies were dental crowding and supernumerary teeth.

Conclusion: Our findings are consistent with previous reports of the prevalence of dental anomalies in individuals with FAP. The results of this study indicate that dental anomalies in individuals with FAP are not consistently recorded in the medical record. Ultimately, consistent documentation of these anomalies in the medical record can aid in detection of FAP in individuals for whom genetic testing is

not available. This highlights the importance of interdisciplinary approaches between clinicians, genetic counselors, and dentists to provide the best and most accurate clinical phenotype description in individuals with FAP.

INTRODUCTION

Familial adenomatous polyposis (FAP) is a rare autosomal dominant hereditary colorectal cancer predisposition syndrome associated with the development of hundreds to thousands of adenomatous colorectal polyps beginning in childhood or early adolescence. Individuals with classic FAP have a very high risk to develop colorectal cancer by age 50 years if the large bowel remains intact (Bussey 1975). Extracolonic manifestations are part of the syndrome and include: epidermoid cysts, osteomas, soft tissue tumors, desmoid tumors, fundic gland polyps, duodenal and small bowel adenomas, congenital hypertrophy of retinal pigment epithelium (CHRPE), and dental anomalies. Individuals with FAP are at risk of developing other malignancies in addition to colorectal cancer. These include small bowel carcinoma (9-12%, typically ampullary or duodenal) (Kadmon et al 2001, Wallace and Phillips 1998), pancreatic carcinoma (approximately 1%; Giardiello et al 1993), thyroid carcinoma (1-12%, typically papillary; Herraiz et al 2007), and hepatoblastoma (less than 2%; Hughes and Michels 1992, Burt 2010). Dental anomalies have long been known to be a feature of Gardner syndrome (Gardner and Richards 1953). While once considered a separate entity from FAP, Gardner syndrome is now considered to be a variant of FAP in which extracolonic manifestations occur together with colorectal polyposis, also caused by *APC* gene mutations.

Approximately 17% of individuals with *APC* gene mutations have dental anomalies (Wijn et al 2005, Brett et al 1994). Specific dental anomalies include tooth agenesis, supernumerary teeth, impacted teeth, and compound odontomas (Ida et al 1981, Brett et al 1994, Wijn et al 2005). The prevalence of supernumerary permanent teeth in individuals with *APC* gene mutations is estimated to be 11%, compared to 0.1% to 3.2% in the general population (Sondergaard et al 1987, Fleming et al 2010). Other reports have suggested that 30% of patients with FAP have supernumerary teeth, compound odontomas, and/or impacted teeth compared to 4% of controls (Wolf et al 1986). Based on these reports we have an imprecise estimate of specific *APC* mutations and dental phenotypes. For at risk individuals, dental anomalies precede the development of adenomatous polyps and can be detected in childhood by clinical oral examination and panoramic radiographs (Antoniades et al 1987, Cahuana et al 2005). In addition to the known association between dental anomalies and FAP, the association of dental anomalies and

predisposition to colon cancer has been previously reported (Lammi et al 2004, Letra et al 2009, Lindor et al 2013).

Published studies indicate that there is a lack of documentation of extracolonic manifestations of FAP in the medical record (Nieuwenhuis and Vasen 2007), but to our knowledge there have not been any studies specifically evaluating medical documentation of dental anomalies in individuals with FAP. In this study we determined the availability of specific dental anomaly information in the physical exam record for individuals with FAP to determine whether this information is regularly recorded at The University of Texas M. D. Anderson Cancer Center (UTMDACC). We then compared the available dental anomalies to data gathered from a dental questionnaire to determine its validity. This allowed us to determine whether there can be improvements in consistent documentation. We also compared the genotype for our individuals with dental abnormalities to previous reports in the literature.

METHODS

Medical Record Review

This study was approved by the institutional review boards (IRB) at UTMDACC and The University of Texas Health Science Center at Houston. All individuals with FAP and a deleterious *APC* mutation or suspected pathogenic *APC* variant and their affected family members who were evaluated between 1995 and 2013 at UTMDACC were eligible to participate in the study. This included both cancer-affected and cancer-unaffected individuals with *APC* gene mutations. Further eligibility criteria were as follows: residence within the United States, age of 8 years or older, and English or Spanish speaking. Individuals were given a unique study-specific identification number to protect their identifying information. Demographic information was obtained from the medical record and a FAP database maintained by the Clinical Cancer Genetics program. The following information was obtained from these sources: current age or age at death, age at diagnosis of FAP, sex, surgical procedure for polyposis, available dental phenotype information, date of last contact at UTMDACC, and *APC* gene mutation and codon. Age of surgical procedure for polyposis was used as the age of diagnosis of FAP if

the diagnosis not specified in the medical records. Surgical procedures for polyposis were classified into the following categories: total abdominal colectomy with ileorectal anastomosis (TAC+IRA), restorative proctocolectomy with ileal pouch-anal anastomosis (PC+IPAA), proctocolectomy with ileostomy (PC+Ileostomy), other, and unknown.

The following was used to classify the date of last contact: 1) deceased, 2) actively followed at UTMDACC (defined as seen within one year of chart review), and, 3) lost to follow-up (defined as not having endoscopic evaluation or clinical appointment at UTMDACC in more than one year since chart review).

Dental phenotype information was collected when it was mentioned in an individual's initial physical exam record at UTMDACC and grouped into the following categories: dental agenesis, supernumerary teeth, misplaced teeth, microdontia, other. Individuals whose physical exam note included a sentence documenting they had denied dental anomalies were recorded as "asked, but no abnormalities noted". The subset of individuals whose note did not mention the patient reporting or denying dental anomalies were recorded as "not asked". Individuals without a detailed physical exam note were recorded as "unknown".

APC genotype was collected from the FAP database. Codons and exons were recorded using either the mutation nomenclature, genetic test result, or the International Society for Gastrointestinal Hereditary Tumours Incorporated (InSiGHT) variant database (http://www.insight-group.org/). InSiGHT database and literature searches were used to determine whether the mutations have been reported previously. Large *APC* gene deletions were categorized by the exon(s) deleted. Intervening sequence (IVS) mutations were grouped collectively. The frequency of each mutation occurring was recorded and the number of families per mutation was tabulated when the same mutation was reported in different individuals.

Dental Questionnaire

A one-page dental questionnaire in either English or Spanish, consent forms, and a pre-addressed, postage-paid return envelope were mailed to individuals who met inclusion criteria and had an address listed. Two questionnaire versions were created: one for children ages 8-15 and the other for ages 16 and older. The consent form specified that parents should fill out the form for children under 18 years old. The questionnaire for ages 16 and older was previously validated in the Cancer Family Registry to ascertain dental history. This questionnaire was also used in a prior study to collect dental anomaly information (Lindor et al 2014). We created an additional questionnaire version that only differed by stated age in the questions. This allowed us to capture children age 8-15 years, as dental anomaly information should be available given that all permanent tooth buds (except third molars) should be visible by age 8 in radiographs. Questionnaires were labeled with the patient's unique, study-specific identification number to link the questionnaire and chart review data. The dental questionnaire consisted of four items intended to assess frequency of dental care, status of permanent teeth (excluding third molars), and self-reported presence of FAP-related dental anomalies. Unclear answers or questions that were left blank were categorized as "not answered" for data analysis. To optimize the response rate, questionnaires were sent twice at approximately one-month intervals. Individuals that returned more than one questionnaire were only counted once.

Data Analysis

The number of patients with available dental anomaly information and the anomalies presented are shown in Tables 1-4. Chi-squared tests were used to test associations between dental anomalies and *APC* gene mutations. The exact calculation option was used because of the small sample size within each group. Statistical significance was set at $P<0.05$ but not adjusted for multiple comparisons. Concordance rate between the medical record and dental questionnaire was tabulated for each anomaly. Individual genotypes with reported dental anomalies were tabulated along with past literature reports of the genotype and any available phenotype information.

RESULTS

Demographic Information

A total of 278 individuals with FAP with either a mutation or suspected pathogenic variant in the *APC* gene were evaluated in the study period. Of these, 260 were eligible for the study and were thus mailed the questionnaire (Figure 1).

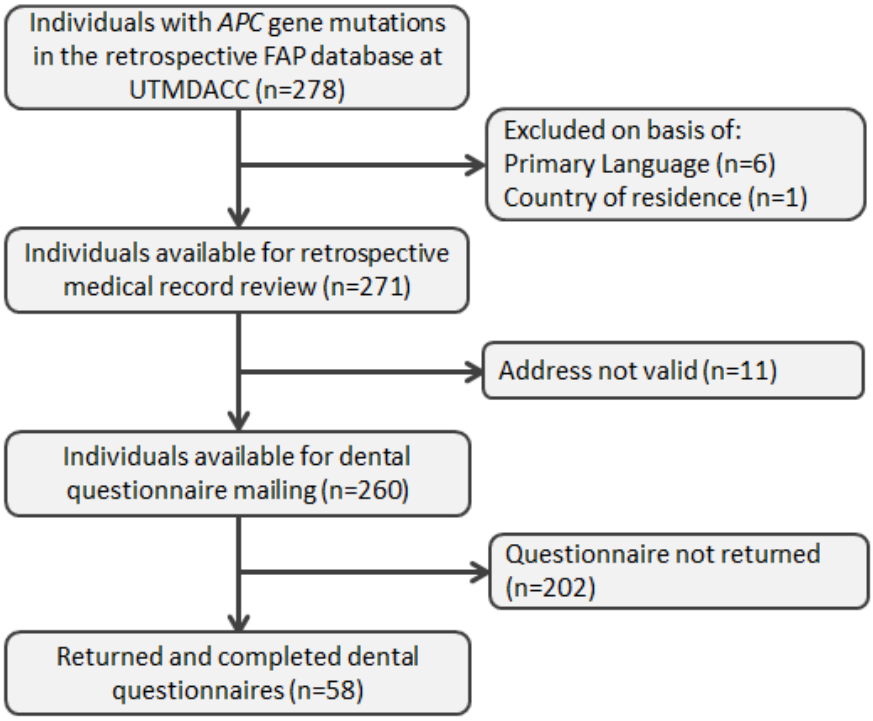

Figure 1. Study flow diagram

Eleven individuals were excluded from the dental questionnaire mailing because their mailing address were no longer valid. Cohort characteristics are presented in Table 1.

Table 1. Cohort characteristics

			Number of Questionnaires Returned	
		All	Yes	No
Demographics	**Characteristic Category**	**N (%)**	**N (%)**	**N (%)**
All		**271 (100%)**	**58 (100%)**	**213 (100%)**
Age at time of questionnaire- median (range)	N=271	40 (9-81)	41 (11-80)	40 (9-81)
Age at diagnosis-median (range)	N=271	24 (0-60)	23 (0-60)	24 (4-59)
Sex	Female	144 (53%)	33 (57%)	111 (52%)
	Male	127 (47%)	25 (43%)	102 (48%)
APC Genetic Test Result	Deleterious mutation	260 (96%)	56 (97%)	204 (96%)
	Variant, suspected deleterious	11 (4%)	2 (3%)	9 (4%)
Language	English	267 (99%)	56 (97%)	211 (99%)
	Spanish	4 (1%)	2 (3%)	2 (1%)
Current Status	Deceased	19 (7%)	0 (0%)	0 (0%)
	Lost to follow-up	150 (55%)	23 (15%)	127 (85%)
	Actively followed	102 (38%)	35 (34%)	67 (66%)
Surgical procedure for polyposis	TAC+IRA †	70 (26%)	17 (29%)	53 (25%)
	TPC+Ileostomy ≠	22 (8%)	6 (10%)	16 (8%)
	TPC+IPAA ‡	44 (16%)	9 (16%)	35 (16%)
	Other*	19 (8%)	6 (10%)	15 (7%)
	Unknown	116 (43%)	20 (34%)	94 (44%)

† TAC+IRA, Total abdominal colectomy with ileorectal anastomosis; ‡ PC+IPAA, Restorative proctocolectomy with ileal pouch anastomosis; ≠ PC+ Ileostomy, proctocolectomy with end ileostomy

***** Subtotal colectomy (n=7), subtotal colectomy with ileal anastomosis (n=2), subtotal colectomy with ileosigmoid anastomosis (n=2), subtotal colectomy with Brooke ileostomy (n=2), subtotal colectomy with small bowel resection (n=1), subtotal colectomy with Hartmann's pouch and end ileostomy (n=1), total colectomy with colostomy (n=2), and low anterior resection (n=2)

The majority of our study group (55%) reported that they undergo dental evaluation twice a year, while only 2% report never undergoing dental evaluation. As shown in Table 1, 96% of the individuals in our study group had a pathogenic mutation, and more than half of individuals in our study group were female. The median age of diagnosis of FAP was 24, with a range from age 0 to 60. Of note, the individual with an age of diagnosis of FAP at 0 years of age was diagnosed via amniocentesis. The majority of the individuals (55%) were lost to clinical follow-up at UTMDACC, while only 7% were deceased. The most common surgical procedure for polyposis was a total proctocolectomy with ileorectal anastomosis, although 42% of individuals did not have surgical information in their medical record.

Figure 2 illustrates the distribution of *APC* gene mutations. As seen in the figure, mutations spanned all exons except exons 1 and 2. There were a total of 270 *APC* gene mutations and of those, 120 were unique familial *APC* gene mutations. Genotype/phenotype correlations were not able to be explored and are instead listed (Supplemental Table 1). The most common mutation was *APC* p.R332X, occurring in 18 individuals from three families.

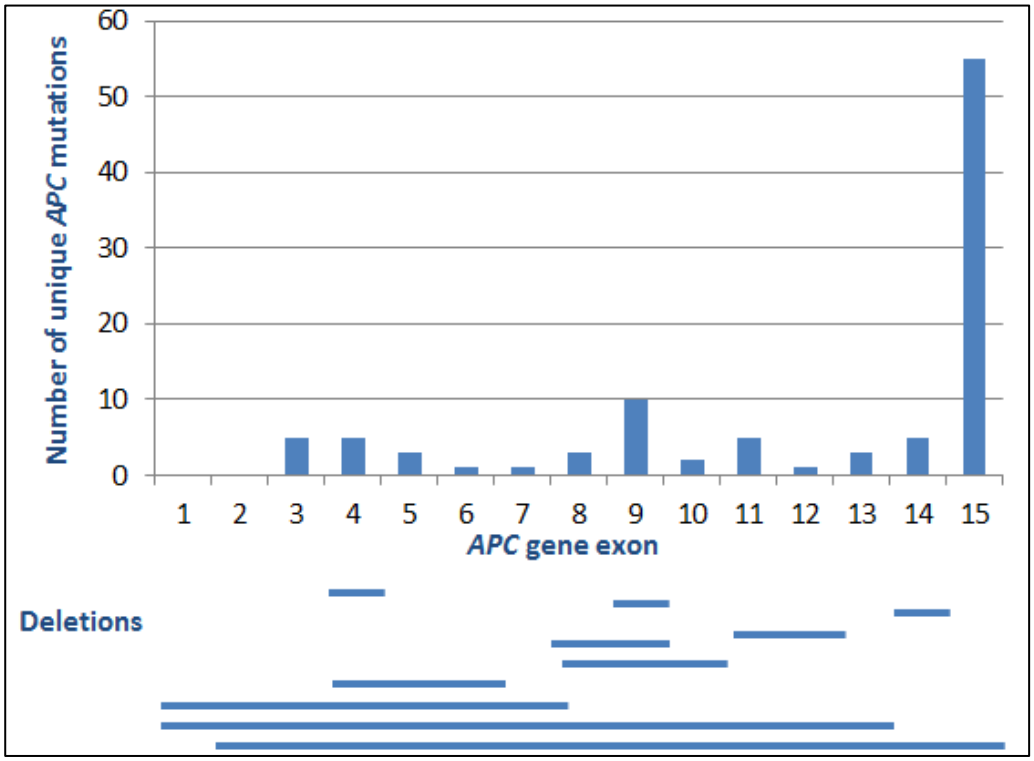

Figure 2. Distribution of mutations in the *APC* gene in individuals with FAP from our study group. A total of 120 unique familial *APC* gene mutations were identified in the study group. Large deletions are depicted under the bar graph as bars spanning the deleted exons of the APC gene.

Supplemental Table 1. *APC* mutations and frequency observed in FAP patient database.

Mutation	Codon	Exon	Frequency	# Families
Codon 77 del 4bp	77	3	1	1
Y96X	96	3	3	2
E100X	100	3	1	1
426delAT	142	3	7	5
Codon 142 delete 2 bp	142	3	2	1
G-1AEx4/ G>A at -1 of exon 4	Unknown	4	2	2
Codon 151 del 1 bp	151	4	1	1
Codon 163 Gln (CAG) to Stop (TAG)	163	4	1	1
502delA	168	4	1	1
530delA	Unknown	4	1	1
573del8	191	5	1	1
Codon 208 Gln (CAG) to stop (TAG)	208	5	1	1
R213X	213	5	4	3
R232X	232	6	3	2
800delG	Unknown	7	1	1
R283X (847C>T)	283	8	1	1
c.904C>T	302	8	1	1
R302X	302	8	1	1
Codon 313 delete 2 basepairs	313	9	1	1
S320X	320	9	1	1
c.935insT	326	9	3	1
p.R332X	332	9	18	3
p.R405X	405	9	2	2
c.1171delA	Unknown	9	2	1
c.1239_1240insA	413	9	1	1
W423X	423	9	5	3
c.1312+5G>A	438	9	1	1
c.1312+3A>G	438	9	1	1
1354-1355delGT/1354delGT	452	10	2	1
S457X	457	10	1	1
Q473X (1417C>T)	473	11	1	1
Codon 479 del 1bp	479	11	1	1
R499X	499	11	2	2
c.1500delT	500	11	2	1
Codon 501	501	11	1	1
1620insA	541	12	5	1
p.W553X	553	13	1	1
R554X	554	13	1	1
Codon 557 deletion 7 base pairs	557	13	1	1
618del16	618	14	4	1
Q625X	625	14	4	1
Codon 626 insert 1 base pair	626	14	2	1
G635X (1903G>T)	635	14	1	1
1907insG	636	14	1	1
1 bp insertion at exon 15	Unknown	15	1	1
Mutation in segment 2	Unknown	15	1	1
c.1967_1974delTAAGAGAG	656	15	1	1
Q695X (2083C>T)	695	15	1	1
W699X	699	15	2	1
2136_2139delTTCA	712	15	1	1
c.2183delA (p.N728IfsX33)	728	15	1	1
S747X	747	15	1	1
2547-2550 del TAGA/2547del4	849	15	4	3
R876X	876	15	3	3
E893X	893	15	1	1
934del4	934	15	1	1
Y935X	935	15	2	2
c.2872A>T (p.R958X)	958	15	1	1

2894delA	965	15	1	1
c.2912insA	Unknown	15	1	1
Q1045X	1045	15	1	1
p.E1047X (c.3139G?T)	1047	15	1	1
W1049X	1049	15	2	2
c.3183_3187delACAAA	1061	15	11	6
Codon 1062 delete 4 bp	1062	15	2	2
Codon 1066 insert 2 basepairs	1066	15	1	1
1067del4, Exon 15	1067	15	5	4
Q1067X	1067	15	1	1
S1068X (3203C>A)	1068	15	2	1
c.3202_3205delTCAA	1068	15	13	5
Codon 1068 Gln (CAA) to stop (TAA)	1068	15	1	1
3255_3256insA	1085	15	1	1
Q1090X	1090	15	1	1
Codon 1101 del 4bp	1101	15	2	1
c.3304_3307delTACA	1102	15	2	1
3366_3369delTCAA	1122	15	1	1
Q1131X	1131	15	1	1
Y1143X	1143	15	2	1
3441insA (Y1147X)	1147	15	5	1
3631-3632delAT	1211	15	2	2
c.3810T>A (p.C1270X)	1270	15	9	2
p.G1288X	1288	15	1	1
I1307K	1307	15	1	1
c.3927_3931delAAAGA	1309	15	9	9
Codon 1342 insert 1 basepair/4026insT	1342	15	2	1
R1450X	1450	15	1	1
4384_4385delAA	1462	15	1	1
1465del2	1465	15	1	1
4389_4390insA/ 4389insA	1468	15	3	1
4348 C>T (Arg1540Ter)	1540	15	1	1
S1545X	1545	15	1	1
4638_4642delTGAAA	1546	15	1	1
E1552X	1552	15	1	1
c.4666insA	1556	15	1	1
4848delA	Unknown	15	1	1
5490_5493delTGAA	Unknown	15	1	1
5933delA, codon 1978delA	1978	15	1	1
c.5936delA	1979	15	1	1
5996delC	1999	15	2	1
del exons 8-9	del	-	1	1
exon 11 and 12 deletion from cDNA	del	-	2	1
del ex 4-6	del	-	2	1
del exons 1-7	del	-	1	1
del exons 2-15	del	-	1	1
deletion exon 8-10	del	-	1	1
del promoter 1B	del	-	1	1
4059_4071delATTTTCTTCAGGA	del	-	1	1
del exons 1-13	del	-	1	1
deletion exon 14 from cDNA	del (14)	-	4	3
exon 15 deletion	del (15)	-	7	2
del exon 4	del (4)	-	11	6
del exon 9 from cDNA	del (9)	-	7	1
IVS10+1delG	IVS	-	1	1
IVS9+3A>G	IVS	-	4	3
IVS4+1G>C	IVS	-	1	1
IVS11+1G>A	IVS	-	1	1
IVS9+5G>A	IVS	-	1	1
IVS3-1G>A	IVS	-	1	1
IVS12+3A>G	IVS	-	1	1
IVS14+1G>A	IVS	-	1	1

Medical Record Documentation

The most common dental anomaly in the medical record was supernumerary teeth (6/271, 2%). The majority (82%) of our study group did not have documentation regarding dental anomalies in the medical record.

Dental Questionnaire

Fifty-eight of 271 (21%) dental questionnaires were completed and returned (Table 2). Thirty-two (55%) individuals self-reported dental anomalies in the dental questionnaire. The most common self-reported dental anomaly was dental crowding in 17/58 (29%) of individuals. This was true for both the older and younger age groups. Individuals with tooth agenesis reported 1-4 teeth missing. Dental anomalies by self-report were denied in 45% (26/58) of individuals. Fifteen percent (23/58) of individuals who were lost to clinical follow-up returned the dental questionnaire compared to 34% (35/58) of actively followed individuals.

Table 2. Results of Questionnaire

		N (%)
Total Completed		**58 (100%)**
Age of participant	8-15 years	14 (24%)
	16+ years	44 (76%)
Dental evaluation (frequency)	Never	1 (2%)
	When I have toothache	9 (16%)
	Once a Year	9 (16%)
	Twice a Year	32 (55%)
	Every 2 Years	3 (5%)
	NA	4 (7%)
Teeth that never formed/missing	Yes	8 (14%)
	No	47 (81%)
	DK	3 (5%)
If Yes, how many	1	3 (38%)
	2	1 (13%)
	3	2 (25%)
	4	1 (13%)
	B	1 (13%)
Tooth agenesis	Yes	7 (12%)
	No	44 (76%)
	DK	1 (2%)
	NA	6 (10%)
Supernumerary teeth	Yes	13 (22%)
	No	41 (71%)
	DK	1 (2%)
	NA	3 (5%)
Microdontia	Yes	4 (7%)
	No	47 (81%)
	NA	7 (12%)
Dental crowding	Yes	17 (29%)
	No	34 (59%)
	DK	1 (2%)
	NA	6 (10%)
NA= not answered; DK=don't know; B=blank		

Medical Record vs. Dental Questionnaire

Table 3 compares the frequency of all self-reported dental anomalies to all documented dental anomalies obtained in the medical record of the 271 individuals in our study. Of the 58 individuals who returned the questionnaire, 10 (17%) also had information about dental anomalies in the medical record.

Of these 10, only 5 (50%) of the answers were completely concordant between the dental questionnaire and medical record documentation.

Table 3. Frequency of dental anomalies obtained from self-report questionnaire and medical record from 271 individuals with FAP

Anomalies		Results N (%)
All Patients	**Questionnaire**	**58 (21%)**
All Patients	**Medical Record**	**47 (17%)**
Tooth agenesis	Questionnaire	7 (12%)
	Medical Record	0 (0%)
Supernumerary teeth	Questionnaire	13 (22%)
	Medical Record	8 (17%)
Microdontia	Questionnaire	4 (7%)
	Medical Record	0 (0%)
Dental crowding	Questionnaire	17 (29%)
	Medical Record	2 (4%)

Dental Anomalies and APC *Genotype*

There were 271 individuals who had deleterious mutations or suspected pathogenic variants and met inclusion criteria. Of these, the most common location was exon 15. There was a statistically significant association between supernumerary teeth reported in the dental questionnaire and *APC* gene exon 15 ($p=0.01$), indicating that individuals with mutations in exon 15 were more likely not to have supernumerary teeth. There was no significant association between any of the dental anomalies recorded in the medical record and *APC* gene exon ($p>0.99$). There was also no association between location of the *APC* mutation and tooth agenesis ($p=0.29$), dental crowding ($p=0.41$), or microdontia ($p>0.99$) from the dental questionnaire.

Table 4 lists self-reported dental anomalies from the dental questionnaire and medical record, as well as the individual's genotype and whether there were any previous reports of the mutation in the literature. The most common mutation associated with dental anomalies in our cohort was *APC* p.W423X, present in four different individuals and three different families with varying dental phenotypes. All individuals in our study with the p.W432X mutation reported having a dental anomaly.

Another common mutation associated with dental phenotype was c.2547_2550delTAGA. Three individuals from two families had this mutation and reported dental anomalies.

Table 4. Distribution of self-reported dental phenotypes and *APC* genotypes in individuals with FAP

Mutation	Codon	Exon	Tooth Agenesis	Dental Crowding	Supernumerary Teeth	Microdontia	Other*	Previously Reported ‡
Total N (%)			**8 (18)**	**19 (43)**	**20 (45)**	**4 (9)**	**6 (14)**	
p.Leu143AlafsX4 (c.426_427delAT)	142	3					X	Friedl and Aretz 2005
p.W423X (c.1268G>A)	423	9		X				Giarola et al 1999
p.W423X (c.1268G>A)	423	9		X		X		
p.W423X (c.1268G>A)	423	9		X	X			
p.W423X (c.1268G>A)	423	9			X			
p.W423X (c.1268G>A)	423	9			X			
p.S457X (c.1370C>A)	457	10		X	X			Wallis et al 1999
p.Q473X (c.1417C>T)	473	11	X					Walon et al 1997
p.Gln541ThrfsX19 (c.1620insA)	541	12			X			Vandrovcova et al 2004
p.Gln541ThrfsX19 (c.1620insA)	541	12			X			
Codon618del16bp (c.1852_1867del16)	618	14	X		X			Su et al 2000
p.Gly637TrpfsX14 (c.1907insG)	636	14			X			Friedl and Aretz 2005
p.W699X (c.2096G>A)	699	15			X			Won et al 1999
p.W699X (c.2096G>A)	699	15			X			
p.Asp849GlufsX11 (c.2547-2550delTAGA)	849	15		X				Miyaki et al 1994
p.Asp849GlufsX11 (c.2547-2550delTAGA)	849	15		X				
p.Asp849GlufsX11 (c.2547-2550delTAGA)	849	15			X			
p.Tyr935IlefsX19 (c.2802_2805delTTAC)	934	15		X	X			Armstrong 1997
p.Tyr935IlefsX19 (c.2802_2805delTTAC)	934	15					X	
p.Y935X (c.2805C>A)	935	15		X				Fodde et al 1992
p.W1049X (c.3146G>A)	1049	15	X	X				Moisio et al 2002
p.Gln1062X (c.3183_3187delACAAA)	1061	15	X					Stella et al 1994
p.Gln1062X (c.3183_3187delACAAA)	1061	15		X				
p.Gln1062X (c.3183_3187delACAAA)	1061	15	X					
Codon1067del4bp (c.3199_3202delCAAT/ p.Ser1068GlyfsX57)	1067	15		X				Ficari et al 2000
p.Ser1068GlyfsX57 (3202_3205delTCAA)	1068	15		X		X		Paul et al 1993
p.Met1211ValfsX5 (c.3631_3632delAT)	1211	15		X				Won et al 1999
p.C1270X (c.3810T>A)	1270	15		X				Su et al 2000
p.C1270X (c.3810T>A)	1270	15			X		X	
p.Glu1309AspfsX4 (c.3927_3931delAAAGA)	1309	15		X				Friedl and Aretz 2005 †

p.Lys1462GlufsX6 (c.4384_4385delAAn)	1462	15					X	Carli Tops (unpublished)
p.Ser1465TrpfsX3 (c.4393_4394delAG)	1465	15		X	X			Miyaki et al 1994
Deletion exon 14	Deletion					X		Su et al 2000
Deletion exon 15	Deletion			X		X		Su et al 2002
c.800delG	Unknown	7	X		X			Not reported
c.1171delA	Unknown	9		X				Not reported
c.4389_4390insA	Unknown	15			X			Not reported
c.4389_4390insA	Unknown	15			X			
Segment 2	Unknown	15	X		X			Not enough information to determine
Deletion exons 1-13	Deletion	1-13			X			Not reported
Deletion exons 8-9	Deletion	8-9					X	Not reported
IVS9+3A>G	IVS	Unknown	X					Not reported
IVS12+3A>G	IVS	Unknown		X	X			Not reported
IVS9+5G>A	IVS	Unknown					X	Not reported

*Other self-reported dental anomalies (and their associated *APC* genotype): enamel hypoplasia (p.Leu143AlafsX4); odontomas (p.Tyr935IlefsX19); osteomas (p.C1270X); osteomas (p.Lys1462GlufsX6); osteomas (Deletion exons 8-9); wisdom teeth removal (IVS9+5G>A)

† Report this at the most common *APC* mutation

‡Previously reported mutations were determined using the InSiGHT *APC* variant database (http://www.insight-group.org/)

DISCUSSION

The current study was undertaken to determine the validity of dental anomalies reported in the medical record compared to self-reported questionnaire in individuals with FAP. We undertook a chart review and distributed questionnaires to evaluate self-reported dental anomalies as well as whether these were documented in the individuals' medical records. A secondary objective of the study was to evaluate possible genotype and phenotype correlations in individuals with FAP and dental anomalies.

A total of 44 out of 271 (16%) of individuals had a self-reported dental anomaly in either the medical record or on the dental questionnaire. This is consistent with previous reports of dental anomalies in approximately 17% of individuals with *APC* gene mutations (Wijn et al 2005, Brett et al 1994). The most frequently reported dental anomalies in our study were supernumerary teeth and dental crowding. The prevalence of supernumerary teeth in our study group of individuals with FAP was 7%,

which is lower than the 11% previously reported in the literature (Sondergaard et al 1987, Fleming et al 2010). Dental crowding was also present in 7% of our study group, which is not surprising given that dental crowding is common in the general population and reported to be prevalent in approximately 24% of the general population (Tschill et al 1997). The frequency of tooth agenesis in our study group, 3%, is consistent with general population reports. The general population prevalence of permanent tooth agenesis varies among studies; however, the prevalence of permanent tooth agenesis (excluding third molars) is approximately 3.2% in males and 4.6% in females of North American Caucasian ancestry (Polder et al 2004). Other studies have reported ranges of 1.6-9.6% for the prevalence of permanent tooth agenesis in the general population (Vastardis et al 1999). The consequences of tooth agenesis are functional and increase in severity with an increase in the number of teeth missing (Polder et al 2004).

In the 44 individuals with self-reported dental anomalies, there were 30 unique *APC* gene mutations. Of these mutations, 21 have previously been reported; however, there have been very few reports that attempted correlated specific *APC* mutations with dental anomalies. For example, the individual in this study with the *APC* mutation p.S457X (c.1370C>A) had dental crowding and supernumerary teeth. This mutation has been reported to be associated dental anomalies, but a precise description of the dental anomalies observed was not included (Wallis et al 1999). Similarly, two individuals in our study had the *APC* mutation p.W699X (c.2096G>A) and both had supernumerary teeth. This mutation has been reported in the literature to be associated with dental anomalies, however no further description of which specific anomaly was included in the report (Won et al 1999). To the best of our knowledge, it appears that 9 of the mutations in our cohort with self-reported dental anomalies have not been previously reported and therefore have not been correlated with dental anomalies. The mutation reported as ‘segment 2’ does not contain enough information to determine whether it has been reported previously. These previously unreported mutations consisted of point mutations, deletions, and insertions that were located in exons 7, 9, and 15. Large deletions spanned exons 1-13 and 8-9. Additionally, three intervening sequence mutations were present.

The dental questionnaire had a response rate 21%. Previous studies assessing self-reported dental anomalies yielded response rates over 50% (Baelum et al 2011); therefore, our response rate was lower than expected. Forty-five percent (26/58) of returned questionnaires indicated an absence of dental anomalies, which may serve to show that there is not a nonresponse bias for individuals without dental anomalies; however, the low response rate may be due to the current status of the cohort of individuals studied. More than half of our cohort (150/271) is not currently being followed clinically at UTMDACC. Interestingly, 15% of individuals that were lost to follow-up at UTMDACC answered and returned their dental questionnaire. This suggests that the population of individuals with FAP continues to stay involved in research, despite not continuing their care with a particular institution. Another possibility for the low response rate was the finite amount of time during which the study was conducted and questionnaires accepted.

Importantly, our study revealed that the majority (82%) of individuals were not asked about dental anomalies during their evaluation, whereas in 42% of individuals their surgical procedure was not documented. This indicates that physicians and/or healthcare providers are not documenting extracolonic manifestations at the same rate they do colonic manifestations. Yet it was surprising to see that in only 58% of individuals was the surgical procedure known. This could, in part, be a reflection on the fact that some of the individuals in this study group presented for counseling prior to genetic testing and not for medical care. Another factor could be that with the advent of genetic testing, health care providers pay less attention to the physical examination in search for extracolonic manifestations. Historically, prior to the availability of genetic testing, benign extracolonic manifestations such as CHRPE, osteomas, epidermoid cysts, osteomas, and dental anomalies in at-risk individuals served to identify patients who most likely had FAP. With today's widespread use of highly accurate *APC* genetic testing to identify asymptomatic carriers, it may be possible that physicians are moving away from documenting extracolonic manifestations, especially those that do not pose a cancer risk. Although dental anomalies are not associated with risk of malignancy, they are important cosmetically and functionally.

We believe that it is important to study the documentation of dental anomalies and other extracolonic manifestations in individuals with FAP. Our large study group of 271 individuals provided a unique opportunity to gather self-reported dental anomaly findings; however, we do recognize that there are limitations in this study. Even though the dental questionnaire was mailed twice, there was a relatively low response rate. The low response rate may have been due to the current status of the cohort of individuals studied. More than half of our study group (150/271) was not currently being followed clinically at our institution. Nevertheless, as mentioned previously, 15% of individuals with lost to follow-up status at UTMDACC answered and returned their dental questionnaire. Due to changes in the storage of medical records over time, it was not possible to obtain phenotype information on all individuals in the short time span of the study (approximately 3 months). Likewise, the amount of time for data collection was finite, thus decreasing the questionnaire response rate. We recognize that we may not have included some individuals with dental anomalies that were mentioned in subsequent notes following their initial history and physical exam. Additionally, we are limited to self-reported findings and did not have the opportunity to study panoramic radiographs to confirm the self-reported anomalies. Future studies on this cohort of individuals would benefit from including a review of panoramic radiographs. Finally, in only 10 patients who returned the questionnaire was there information in the medical record to correlate self-response with objective data. The number of responses and medical documentations were too small to make meaningful conclusions regarding the self-reporting and medical record documentation correlation.

It is clear from medical record review that there is a lack of documentation of dental anomalies in the medical record of individuals with FAP. Many different terms are used to describe dental anomalies in individuals with FAP. Healthcare providers should use consistent terms to describe dental anomalies in individuals with FAP to ensure consistency between studies. Our results suggest that it may benefit healthcare providers that care for individuals with FAP to create a phenotype checklist that includes consistent terms for dental anomalies, as well as other extracolonic manifestations to ensure proper documentation and follow-up. We propose that this list of dental anomalies should include

supernumerary teeth, tooth agenesis, microdontia, dental crowding, and an 'other' category. These anomalies should ideally be confirmed by both intraoral examination and panoramic radiograph performed by a dentist. Our data also suggests that it is important to ask individuals with FAP whether they have specific dental anomalies. We can surmise that if individuals are simply asked if they have any dental anomalies, in general they will deny it; whereas, if they are asked about a specific anomaly or anomalies they can individually report or deny them. It is also important to document a negative history of dental anomalies, as this is also pertinent phenotype information and shows that the healthcare provider has conducted a thorough medical evaluation.

CONCLUSION

Our data suggest that it is important to keep an accurate record of the presence and/or absence of specific dental anomalies in individuals with FAP and their family members. These results also highlight the importance of interdisciplinary approaches between clinicians, cancer geneticists, and dentists to provide the best and most accurate clinical phenotype description in FAP patients. In individuals for whom genetic testing is not available, documentation of extracolonic manifestations including dental anomalies may provide earlier evidence of underlying FAP and result in intense surveillance for these individuals to reduce the risk of malignant transformation of adenomatous polyps. The early identification of dental anomalies may represent an additional and inexpensive screening tool.

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