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Frequent gastrointestinal polyps and colorectal adenocarcinomas in prospective series of *PTEN* mutation carriers

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Abstract

BACKGROUND & AIMS—Germline *PTEN* mutations cause Cowden syndrome (CS), associated with breast and thyroid cancers. Case reports found 35–85% of CS patients had gastrointestinal (GI) hamartomas. The association of benign and malignant GI neoplasias with CS remains debatable. Our goal is to describe the GI phenotype in a prospective series of *PTEN* mutation carriers.

METHODS—Patients who met relaxed International Cowden Consortium criteria (N=2548) or with ≥5 GI polyps, ≥1 of which was hyperplastic or hamartomatous (N=397) were prospectively

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recruited. Germline *PTEN* mutation/deletion analysis was performed. Of the 2945, 127 patients having clear pathogenic *PTEN* mutations (123/2548+4/397) were eligible for this study. EGD and colonoscopy were performed and pathology reports reviewed. Fisher's 2-tailed exact test, unpaired t-tests, and age- and gender-adjusted SIR were calculated.

RESULTS—Of 127 *PTEN* mutation carriers, 67 underwent ≥1 endoscopy with 62 (95%) having polyps, making GI polyps the second most common feature, after macrocephaly (74.8%). Of the 65, half had hyperplastic polyps and ¼ each with hamartomatous, ganglioneuromatous or adenomatous polyps. There were one to "innumerable" polyps in the colorectum, ileum, duodenum, stomach and/or esophagus, with 24 subjects having both upper and lower GI polyps. Nine (13%) subjects had colorectal cancer, all under the age of 50. The adjusted SIR was 224.1 (95%CI 109.3–411.3, p<0.0001). Cancers were commonly associated with adenomatous and/or hyperplastic polyps. One had gastric signet ring cell carcinoma.

CONCLUSIONS—*PTEN*-associated CS should be considered a mixed polyp syndrome, with hyperplastic polyps most prevalent, and a risk of early-onset colorectal cancer. Routine colonoscopy should be considered in *PTEN*-associated CS especially in the context of hyperplastic and/or adenomatous polyps.

Keywords

colorectal cancer; Cowden syndrome; hamartomatous polyposis; *PTEN*

Background

Cowden syndrome is often considered a rare hamartomatous polyposis syndrome caused by germline alterations in the tumor suppressor gene, *PTEN*.[1] It is thought to occur in 1 in 200,000 individuals; however, experts believe this is likely an underestimate because of the variable expression and subtle physical manifestations.[2] CS is one of the disorders that comprises the PTEN hamartoma tumor syndrome.[3] It is an autosomal dominant disorder that is characterized by mucocutaneous lesions, macrocephaly, and an increased risk of benign and malignant diseases of the breast, thyroid, and endometrium.[2, 3] Although the gastrointestinal (GI) tract is affected in individuals with CS, it has not been systematically assessed.

Published case reports and highly selected small series reveal that 35–85% of Cowden syndrome patients had GI hamartomatous polyps.[4–9] Although the majority of patients have been described to have hamartomatous polyps, they have also been reported to have ganglioneuromatous polyps, colonic lipomas and lymphoid aggregates, and hyperplastic, adenomatous, and inflammatory polyps. These polyps have been reported to occur in the esophagus, stomach, duodenum, jejunum, ileum, colon and rectum, with the colon being the site most often affected.

Whether GI neoplasias, especially malignancies, are true component phenotypes of CS is not known because this association has not been systematically studied in large series.[10] Various case reports of colorectal cancer in patients with CS have been published, mainly prior to the mid-2000's and often without the advantage of *PTEN* mutation status.[5, 11–13] In a series of 93 Japanese patients, nine (9.6%) were reported to have colon cancer.[14] Gastric cancer has been highlighted in case reports of two individuals with CS.[15, 16] The risk of benign and malignant GI neoplasias has yet to be characterized in a large series of individuals with *PTEN* mutation positive Cowden syndrome. We, therefore, sought to determine the prevalence and characteristics of the GI phenotype in our series of *PTEN* mutation positive subjects.

Materials and Methods

Study Design

Between October 2005 and June 2009, subjects were prospectively recruited into a DNA banking protocol approved by the Institutional Review of Board for Human Subjects' Protection of the Cleveland Clinic. Subjects were selected from enrollees from two systematic prospective cohorts: (1) those who met relaxed International Cowden Consortium (ICC) operational criteria (a pathognomonic mucocutaneous lesion, at least one major criterion with or without minor criteria, or at least two minor criteria) or (2) those who had at least five gastrointestinal polyps, at least one of which must have been hyperplastic or hamartomatous (see schema in Figure 1). Enrollees into these two protocols originate from primary care clinics in the community setting to genetics or oncology clinics in academic medical centers throughout North America and Europe. Upon providing informed consent, subjects provided a DNA sample and self-reported personal and family medical history. When available, medical records documenting the subject's history of neoplasias were obtained. All subjects underwent mutation analysis of the *PTEN* gene, and only those found to have a deleterious germline mutation were included in this present study. Subject medical records were reviewed for any endoscopy (EGD and/or colonscopy) records and surgical pathology reports documenting gastrointestinal neoplasms (polyps, carcinoma), and those findings are reported descriptively.

PTEN Mutation Analysis

Genomic DNA was extracted from peripheral blood leukocytes. Intragenic *PTEN* was analyzed with a combination of PCR-based DGGE and direct sequencing (ABI 3730xl) as previously reported.[17] *PTEN* promoter mutations and large deletions/ rearrangements were assessed as previously described.[18]

Statistical Methods and Data Analysis

Fisher's 2-tailed exact test and unpaired T-tests were utilized for comparison of *PTEN* mutation positive patients with and without polyps. An age- and gender-adjusted standardized incidence ratio (SIR) was calculated to compare incidence of colorectal and gastric cancers in our series to that of the Surveillance Epidemiology and End Results (SEER) database.

Results

Patients who met relaxed International Cowden Consortium (ICC) criteria (N=2548) or with ≥5 GI (any location) polyps, ≥1 of which was hyperplastic or hamartomatous (N=397) were prospectively recruited (see schema in Fig. 1). Of the 2945 total subjects from these two prospectively accruing protocols (see Methods for details), 127 patients having clear pathogenic *PTEN* mutations were eligible for this study (Fig. 1). Four of these subjects were enrolled from the cohort ascertained by presence of at least five GI polyps, at least one of which was hyperplastic or hamartomatous, and the remaining 123 were enrolled from those who met relaxed ICC criteria (Fig. 1). In our series of 127 *PTEN* mutation positive individuals, there were 8 individuals who might be clinically diagnosed with BRRS, comprising 5 male individuals with penile freckling and macrocephaly, 3 of whom also had lipomatosis. The remaining 3 were females, all of whom had macrocephaly, at least one lipoma (not lipomatosis) and one vascular anomaly. None of these 8 had GI malignancies. Average age at study enrollment was 34.6 years (range 1–73 years), and 63 (49.6%) were male. The majority of subjects were white (78), of which 4 were Hispanic/Latino, with the remaining black or African American (9), American Indian or Alaska Native (8), or Asian (6). Race was unknown for 26 subjects.

Of the 127 eligible subjects, GI polyps were reported in 65 (51.2%), with 24 having both upper and lower GI polyps, two only upper GI polyps and 41 only colorectal polyps. Subjects with polyps were significantly older (42.0 years) at the time of enrollment compared to those without polyps (26.6 years, p=0.0001). No gender differences were observed between those with and those without polyps. There was no clear genotype-phenotype correlations for those with or without polyps or those with or without malignancies.

Colorectal Polyps and Carcinomas

At least one colonoscopy was performed for 67 (52.8%) subjects. The average age at first colonoscopy was 36.4 years (1–73 years). Twenty patients underwent colonoscopy because they were symptomatic (abdominal pain, bleeding, constipation, protein-losing enteropathy); eight had the procedure because of the diagnosis of CS; seven underwent a general population screening colonoscopy; seven were due to a personal/family history of polyps; and two for other reasons (rectovaginal fistula and history of cervical cancer). For 23 subjects, the reason for the procedure was unknown. Only four patients had a normal GI examination. Colorectal polyps were identified in 62 subjects (representing 95% of those who underwent ≥1 colonoscopy, or 49% of all eligible subjects) and nine (representing 13% of all who underwent ≥1 colonoscopy, or 7.1% of all eligible subjects) had adenocarcinomas, with one, a rectal cancer, and the remaining 8, colon cancers (Table 1).

The lower GI polyps were found throughout the colon and rectum (Table 1). Of the 62 subjects with colorectal polyps, 18 were found to have hamartomatous polyps, 27 hyperplastic, 16 ganglioneuromatous, 16 adenomatous, and 11 inflammatory (Table 1). At least nine subjects had polyps of three different histologic types. Of the 27 subjects with colorectal hyperplastic polyps, at least 16 meet the operational diagnosis of hyperplastic polyposis syndrome.

The nine colorectal cancers were diagnosed in five females and four males (Table 1). The average age at diagnosis was 44.4 years (range 35 to 49 years). Notably, the age- and gender-adjusted SIR for colorectal cancer in our series was 224.1 (95% CI 109.3–411.3, p<0.0001). One subject, 2466, presented with colorectal adenocarcinoma in the absence of polyps, and never went on to develop polyps. Three individuals with adenocarcinomas were found to have synchronous adenomatous polyps. In other words, of the 16 individuals with adenomatous polyps, three (18%) developed colorectal cancer. Two of these three individuals with adenomatous polyps and colorectal cancers also had hyperplastic polyps. Five individuals with colorectal carcinomas each had multiple (non-adenomatous) polyps, chief of which were hyperplastic (Table 1). Said another way, of the 27 subjects with hyperplastic polyps, four (15%) had colorectal carcinomas. Three of these four individuals meet the clinical diagnosis of hyperplastic polyposis as well.

Upper Gastrointestinal Findings

Thirty-nine (30.7%) subjects underwent at least one EGD. The average age at first EGD was 39.7 years (2–73 years). The most common indication for undergoing EGD were symptoms including weight loss (N=1), abdominal pain (3), esophagitis (1), gastroesophageal reflux disease (2), vomiting (1), dysphagia (4), diarrhea (2), hematochezia (1), anemia (1), and GI symptoms that were not otherwise specified (1). Five subjects had the examination because of the diagnosis of Cowden syndrome, six because of a history of colonic polyps, nine for unknown reasons, and two for other reasons (history of ulcerative colitis and an abnormal CT scan). Of the 39, only one subject had a normal examination. Gastritis or inflammation was present in 7 (17.9%) subjects and 8 (20.5%) had glycogenic acanthosis (Table 2). Upper GI polyps were found in 26 (66.7%) subjects within the esophagus, stomach, and duodenum

(Table 2). Only two individuals had fundic gland polyps. Additionally, Subject 985, who was white Caucasian, was diagnosed in the late 60's with invasive moderately to poorly differentiated adenocarcinoma with signet ring features arising in a large hyperplastic/ hamartomatous gastric polyp. Although only a single individual, age- and sex-adjusted SIR for gastric cancer in this series is 148 (7.4–733, p<0.001). This individual also had diffuse hyperplastic polyposis of the upper (and lower) tracts.

Cowden Syndrome Clinical Features

Clinical features characteristic of or suspicious to be part of Cowden syndrome were also recorded for all 127 subjects (Table 3). As a control, we note that breast cancer occurred in ~37% (age- and sex-adjusted SIR~22, p<0.001) and thyroid cancer 16.5% (adjusted SIR~65, p<0.001) of these *PTEN* mutation carriers, within the ranges of previous estimates and the single population-based clinical epidemiologic study by Starink.[3, 19] Macrocephaly was found in the great majority and was the most common clinical feature in our series of *PTEN* mutation carriers (95 [74.8%]). Somewhat surprisingly, GI polyps occurred in 51.2% of all eligible subjects or 95% of eligible subjects undergoing at least one colonoscopy, making them the second most common phenotypic feature only after macrocephaly.

Discussion

Recognition of pertinent personal medical and family history features as well as physical manifestations is critical for accurate diagnosis, risk assessment, genetic testing, and medical management for individuals with hereditary cancer syndromes. Textbooks and single case reports have noted the association of CS and hamartomatous polyps for some time, but not necessarily based on systematic analysis. However, it remains an under-acknowledged manifestation of the disorder for several reasons, perhaps because the malignant potential of these polyps is not well characterized and because there has yet to be a systematic series addressing even the frequency and characteristics of the polyp histology. In our series of all comers with germline pathogenic *PTEN* mutations, GI polyps occurred in 51.2%, making it the second most common CS feature. Considering that colorectal polyps occurred in 95% of our eligible subjects with germline *PTEN* mutations who underwent at least one colonoscopy, and approximately half of the entire series, this 51.2% prevalence of any GI polyp is likely an underestimate. Notably, in addition to the textbook-acknowledged hamartomatous polyps, we show here that hyperplastic polyps, ganglioneuromatous polyps and adenomatous polyps are important components of the CS polyp histology. In fact, at least half of our mutation carriers who were shown to have colorectal polyps had two or more histologic types.

In an effort to create uniform criteria in 1995 for the purposes of identifying the predisposition gene, the ICC developed consensus operational diagnostic criteria,[20, 21] which were revised in 2000, in an attempt to broaden the net for clinical usage.[2] These criteria specify that GI hamartomas are a minor criterion because of lack of systematic study. If the ICC criteria were amended to include GI polyps as a major criterion, then an additional 21 (16.5%) subjects would have had a clinical diagnosis of Cowden syndrome at the time of study enrollment. The most recent version of the National Comprehensive Cancer Network Cowden syndrome testing criteria were updated to include multiple GI hamartomas or ganglioneuromas as a major criterion and a single GI hamartoma or ganglioneuroma as a minor criterion based on expert opinion in the context of single case reports and highly selected small series, often without *PTEN* mutation information.[22] The observations from our prospective systematic study lend objective support to the changes to the NCCN testing criteria.

For patients who are suspicious for the *PTEN* hamartoma tumor syndrome, it is important to assess previous history of GI polyps. Efforts should be made to confirm the polyp burden in these patients with medical records. Additionally, given the inaccuracies with polyp histology,[23] consideration should be given to having the pathology re-reviewed by a dedicated GI pathologist. For patients suspicious for Cowden syndrome or a *PTEN* hamartoma tumor syndrome who have not previously undergone an endoscopy, the risks and benefits of a baseline upper endoscopy and colonoscopy should be considered in the diagnostic workup.

Colorectal cancer occurred in 7.1% of our entire series and 13% of eligible subjects who underwent at least one colonoscopy (age- and gender-adjusted SIR=224). Currently, colorectal surveillance is not routinely recommended for individuals with Cowden syndrome beyond that for the general population. However, in our series, all nine subjects were diagnosed with colorectal cancer prior to age 50, with the youngest age at diagnosis being 35 years. Therefore, had our subjects initiated screening at age 50, their malignancies would likely not have been detected until an advanced stage. Individuals with *PTEN* mutations may benefit from earlier colonic surveillance. One group has advised a “vigorous” screening approach to patients with Cowden syndrome that includes colonoscopy beginning at age 15 with follow up every 1–2 years.[24] This approach is rather aggressive. Based on our current observations, we recommend considering a baseline colonoscopy at age 35, or sooner if symptoms develop, with follow-up time based on polyp burden.

Based on our series, ~15% of *PTEN* mutation carriers with colorectal hyperplastic polyps developed colorectal cancer; and almost 20% of mutation carriers with colorectal adenomas had colorectal cancer. The patients who developed colorectal carcinomas also tended to have multiple polyps, based on small numbers. Therefore, if these observations can be reconfirmed in an independent series, then indications for colorectal surveillance should be offer to any *PTEN* mutation carrier with multiple lower GI polyps, and/or the presence of hyperplastic and/or adenomatous polyps.

There were 2 (13%) individuals with sessile serrated adenomas, both of whom were amongst the 16 individuals who met the criteria for hyperplastic polyposis syndrome. There are 2 interpretations to this observation: that this is a true representation, or there was uneven “calling” of this histology amongst the pathologists. We tried to gauge this by culling out our research subjects enrolled in another study (who may or may not have *PTEN* mutations) during a similar period, and we found that of those who met the diagnosis of HPS, ~50% also had sessile serrated adenomas (p=0.07).

Only one individual in our series developed gastric cancer. Although the formal adjusted SIR is elevated, we cannot draw genetic counseling or clinical conclusions given that this single subject was a white male who developed gastric cancer at 67 years old. It is nonetheless interesting to note the co-existing diffuse hyperplastic polyposis in the stomach and duodenum, almost mirroring the situation in the colon. In our series of *PTEN* mutations carriers, upper GI polyps do occur with some frequency, and, for a subset of patients, they do experience symptoms. Excluding the five individuals with unknown polyp histology in the upper GI tract, 15 of the 19 with polyps in the upper and lower tracts had concordant histologies. Interestingy, fundic gland polyps, often said to be indicative of CS, were only found in two mutation carriers. Notably, 20% of those with GI examinations had glycogenic acanthosis. Although no consensus guidelines exist regarding upper GI management in CS, Schreibmann *et al.* recommend upper endoscopy and an upper GI series with small bowel follow-through beginning at age 15 with follow up every two years.[24] Again, based on our current observations, we believe that this approach is rather aggressive and recommend upper GI surveillance only for symptom management, at least in the white population. Based

on anecdotal reports on Asian populations, we suspect that GI features, perhaps even upper GI malignancies, may be more prominent in the Asian population.

One of the major limitations of this study is that not all medical records were available to confirm all of the reported histories, although these remain in the minority. Therefore, for some patients, we do not have detailed information about their precise GI history. Further, since patients were recruited from multiple medical centers, there is wide variability in the medical reports and pathology expertise available. The most ideal study would be to offer at least baseline colonoscopy, by a limited number of endoscopists, and to have the pathology reviewed by a single pathologist with expertise in hereditary GI disease in order to accurately capture the frequency with which GI polyps occur in these patients. Nonetheless, despite these limitations, the conditions of the study do somewhat simulate the data available at a high-risk GI consultation.

Based on the observations from our prospectively accrued series of *PTEN* mutation carriers and the literature, we conclude that both upper and lower GI polyps are common component features of the *PTEN* hamartoma tumor syndrome. The presence of non-adenomatous polyps, and especially comprising mixed histologies, should signal a healthcare provider to refer such individuals to high-risk assessment. Furthermore, the presence of both macrocephaly and non-adenomatous GI polyps together should predict, to a high probability, for the presence of germline *PTEN* mutations. Colorectal adenomas are usually not considered part of the CS phenotype, but our series suggests that they most likely are, with almost 20% of *PTEN* mutation carriers with colorectal adenomatous polyps developing colorectal adenocarcinomas. Similarly, multiple colorectal polyps of any histology and hyperplastic polyps, especially a hyperplastic polyposis syndrome phenotype, may be red flags for *PTEN* mutation carriers developing colorectal cancers. Importantly, colorectal adenocarcinomas have an increased prevalence in *PTEN* mutation carriers, all occurring prior to the age of 50 years, and so, routine colonic surveillance should be considered.

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Abbreviations

CS	Cowden syndrome
EGD	Esophagogastroduodenoscopy
FGP	fundic gland polyps
GI	gastrointestinal
ICC	International Cowden Consortium
SSP	sessile serrated polyps
SIR	standardized incidence ratio

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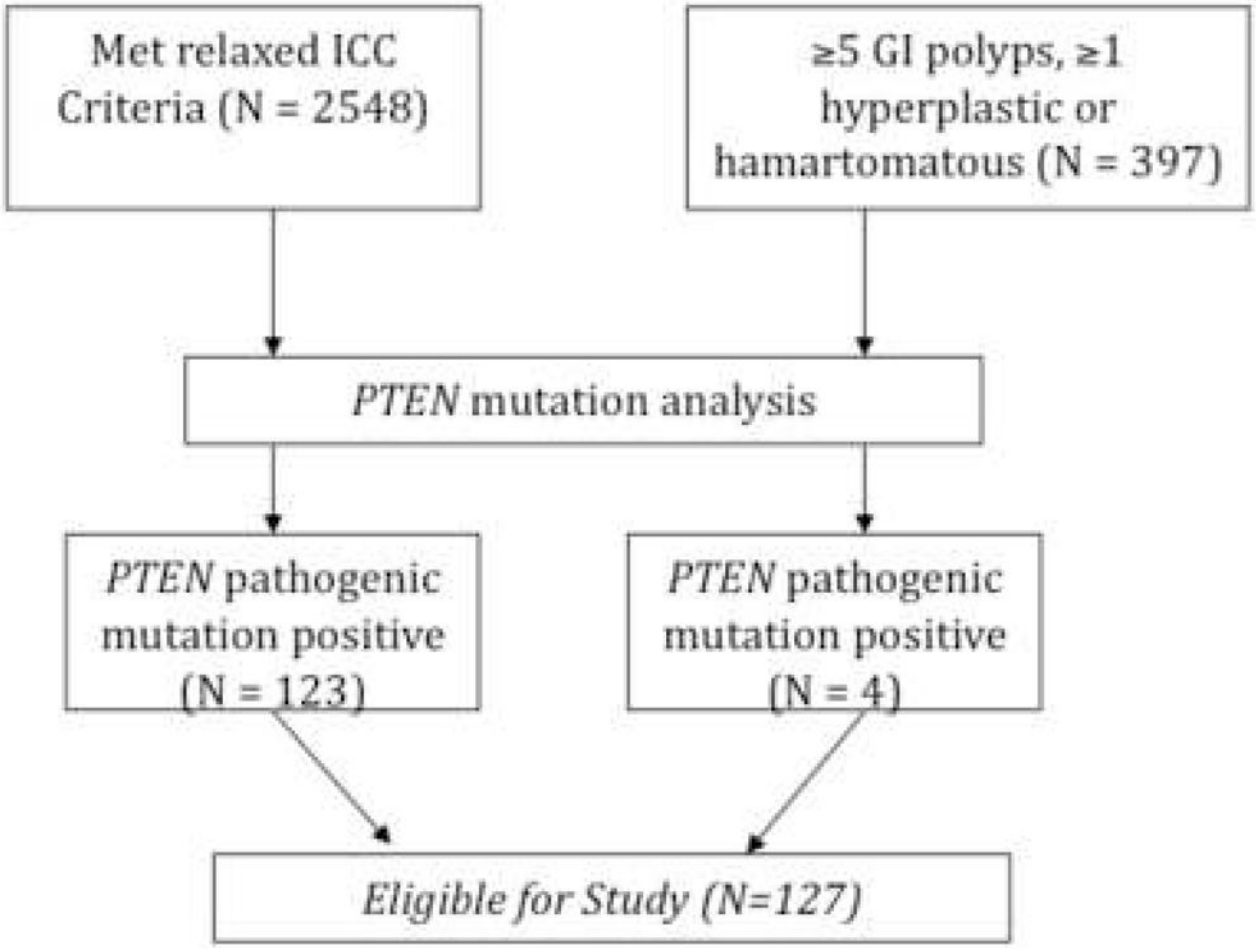

Figure 1.
Schema for the prospective accrual of individuals meeting relaxed ICC criteria or the 5-polyp criteria and carrying clear pathogenic *PTEN* mutations. To be conservative, individuals with variants of unknown significance or promoter variants were excluded.

Table 1

Colorectal polyps, their histology a nd colorectal adenocarcinomas in *PTEN* mutation carriers

Subject	***PTEN* mutation**						
		Hamartom	**Hyperplastic**	**Ganglioneur**	**Adenoma**	**Inflamm**	**Other**
1306-3	IVS6+2T>C	1					
3159	R335X	1					
2834	Q17X	10					
1515	P95L	>50					
68	302delT	Multiple					
651-2	461delT	Multiple					
3349	512insA	Multiple					
86	470insG	Numerous					
451	R335X	Multiple					
547	PTEN/BMPR1A deletion	Multiple					
2782	26delT	Multiple					
521-2	R130X	Multiple					
178	R130X	1	2	1			
3015	734del4	2		3			
2381	C211X	Multiple	Multiple				
1824-1	Exon 2 deletion	Multiple	Multiple				Lipomas
3028	10q23.2–10q23.31 deletion	Numerous		Numerous	Numerous		
385	592_601del10	Numerous	Numerous	Numerous	Numerous		LA
3007	R159T		1				
393	M35V		4				
2447	C136R		9				
2736	R173C		Multiple				
1879	R355X		2	Carpeting			
2224	R335X		2		2		
958	Exon 1 deletion		5		2		
1140	G132D		3		2	1	2SSP

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Subject	*PTEN* mutation						
		Hamartom	Hyperplastic	Ganglioneur	Adenoma	Inflamm	Other
1083	19insCT		2			6	Lipomas
2438	L345V		3				LA
1968	209+1G>T		Multiple	Multiple	Multiple		LA
3605	210-2_211delAGTT		Multiple	Multiple		Multiple	Adenocarcinoma
417	350insA		3		Pan- colonic		Adenocarcinoma
907	895insTA		Multiple		1		
2127	Y240X		Carpet		2		Adenocarcinoma
237-2	C136Y		Numerous		Numerous		
3577	L181P		Multiple		Multiple	Multiple	
1824-2	Exon 2 del		Multiple		Multiple	Multiple	
723	542delT		Multiple		Multiple	Multiple	
985	1019delA		Multiple			Multiple	
111	R130X		Innumerable				Lipomas
294	1027-2A>C		Multiple				Adenocarcinoma
37	C211X		Multiple				Adenocarcinoma
1694	1026+1G>C			>3			
3935	R130X			>40			Adenocarcinoma
622	C136R			Multiple			
2370	491delA			Multiple			
139	253+1G>A			Numerous			
2544	407del17			Numerous			
2539	968delA			Numerous		4	
1094	635-1G>C			Numerous		Numerous	
47	R130X			Multiple		Multiple	Adenocarcinoma
559	R130Q				1		
2986	R233X				13		Adenocarcinoma
1027	A120E				Multiple	Multiple	
1306-1	IVS6+2T>C						30-40 SSP; LA

Subject	*PTEN* mutation						
		Hamartom	**Hyperplastic**	**Ganglioneur**	**Adenoma**	**Inflamm**	**Other**
77	S229X						Polypoid mucosa
2466	H61R						Adenocarcinoma
1334-2	210-1G>A						1 polyp, unknown path
1495	R335X						2 polyps, unknown path
1334	210-1G>A						50-100 polyps, unknown path
180	P96R						Many polyps, unknown path
4-3	G219X						Polyps, unknown path or number
367	870delA						Polyps, unknown path or number
2613	406insA						Polyps, unknown path or number

Quantitation of polyps derives from endoscopy reports.

Hamartom, hamartomatous polyps; Hyperplastic, hyperplastic polyps; Ganglioneur, ganglioneuromatous polyps; Adenoma, adenomatous polyps; Inflamm, inflammatory polyps; LA, lymphoid aggregates; path, pathology; SSP, sessile serrated polyps.

Note that Subject 37 has previously been reported in the literature.[13]

Table 2

The number of polyps and corresponding pathology of the upper GI polyps found in *PTEN* mutation positive carriers

Subject	*PTEN* mutation					
		Hamarto	Hyperplastic	Ganglioneur	Adenoma	Other
68	302delT	1-5				
1306-1	IVS6+2T>C	Multiple				
3349	512insA	Multiple				
521-2	R130X	Multiple				
3028	10q23.2–10q23.31 deletion	Few		1		
912	R130X	Several			2	Polypoid mucosa
393	M35V		3		Multiple	
417	350insA		Multiple			
165	48insA		Innumerable			
1027	A120E		Myriads			
1140	G132D		Multiple			Few FGP
2782	26delT		Multiple			Multiple inflammatory pol
985	1019delA		Diffuse			Adenocarcinoma; FGP
1083	19insCT		Multiple			Multiple inflammatory polyps
2370	491delA			Multiple		
178	R130X					Polypoid mucosa
1879	R355X					Polypoid mucosa
294	1027-2A>C					Polypoid mucosa
723	542delT					Polypoid mucosa
47	R130X					Polypoid mucosa
86	470insG					Polypoid mucosa
180	P96R					Many polyps, unknown path
2381	C211X					Many polyps, unknown path
2986	R233X					Multiple polyps, unknown path
2834	Q17X					Multiple polyps, unknown path
37	C211X					100s polyps, unknown path

Quantitation of polyps derives from endoscopy reports.

Hamartom, hamartomatous polyps; Hyperplastic, hyperplastic polyps; Ganglioneur, ganglioneuromatous polyps; Adenoma, adenomatous polyps; FGP, fundic gland polyps; path, pathology

Table 3

Frequency of Cowden syndrome features observed in our *PTEN* mutation positive series

Cowden Sydrome Feature	Frequency (percentage)
Macrocephaly	95 (74.8)
GI Polyps	65 (51.2)
Goiter/thyroid nodules	56 (44.1)
Benign breast disease *	24 (37.5)
Breast cancer *	24 (37.5)
Lipomas	44 (34.6)
Papillomatous papules	43 (33.9)
Endometrial fibroids *	17 (26.6)
Trichilemmomas	26 (20.5)
Penile freckling ^	12 (19.0)
Acral keratoses	21 (16.5)
MR/DD	21 (16.5)
Thyroid cancer	21 (16.5)
Endometrial cancer *	8 (12.5)
Colorectal cancer	9 (7.1)
Lhermitte-Duclos disease	8 (6.3)
Autism	8 (6.3)

Note that GI polyps are the second most common feature.

* female subjects only;

^ male subjects only.