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Expanded Extracolonic Tumor Spectrum in *MUTYH*-Associated Polyposis

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See editorial on page 1883.

BACKGROUND & AIMS: *MUTYH*-associated polyposis (MAP) is characterized by a lifetime risk of colorectal cancer of up to 100%. However, no systematic evaluation of extracolonic manifestations has been reported. **METHODS:** A large cohort of MAP patients was recruited from a European multicenter study. Data were collected on 276 cases from 181 unrelated families. Information on extracolonic tumor spectrum and incidence were evaluated to determine cumulative lifetime risk, which was compared with that of the general population to obtain standardized incidence ratios (SIRs). **RESULTS:** Duodenal polyposis occurred in 17% of cases; the relative risk (SIR) of duodenal cancer was 129 (95% confidence interval [CI]: 16–466), whereas the lifetime risk was 4%. The incidence of extraintestinal malignancies among cases was almost twice that of the general population (SIR: 1.9; 95% CI: 1.4–2.5), with a lifetime risk of 38%. We observed a significant increase in the incidence of ovarian, bladder, and skin cancers (SIR: 5.7, 7.2, and 2.8, respectively) and a trend of increased risk of breast cancer among cases. The median ages of onset of these 4 malignancies ranged from 51 to 61 years. In contrast to familial adenomatous polyposis, no desmoid tumors were observed, but sebaceous gland tumors, characteristic of the Muir-Torre variant of Lynch syndrome, occurred in 5 patients. **CONCLUSIONS: The relative risks for several extraintestinal malignancies increased in patients with MAP, but based on the spectrum of cancers (which overlaps with that of Lynch syndrome) and the relatively advanced age at onset, intensive surveillance measures other than frequent endoscopy are unlikely to be helpful to patients with MAP.**

MUTYH-associated polyposis (MAP) (OMIM #608456) is recognized as an autosomal recessive disorder associated with adenomas and cancers of the colorectum. It is caused by biallelic germline mutations in the base excision repair gene *MUTYH* (*MYH*) that lead to an increase in 8-oxoG–induced somatic G:C>T:A transversions in other genes, including tumor suppressors such as the *APC* gene.

The condition was described for the first time in 2002.[1] During recent years, the colorectal phenotype has been delineated in different groups of patients.[2–12] MAP is characterized by the appearance of multiple adenomas throughout the colorectum, usually numbering between dozens and a few hundreds. The attenuated or atypical form of familial adenomatous polyposis (FAP) is the most important differential diagnosis (for review see Galiatsatos and Foulkes[13]). Colorectal adenomas or colorectal cancer (CRC) usually become symptomatic between the 4th and 7th decade of life,[2,5,6,8] and the cumulative lifetime risk for CRC has been estimated to be up to 100%.[14] Recently, a robust correlation has been established between the most frequent *MUTYH* genotypes and the severity of colorectal polyposis and age-related risk of CRC.[15]

In contrast to the colorectal phenotype, there is little information on the spectrum of extracolonic manifestations in MAP. In up to one-quarter of cases the duodenum is affected,[2,5,12] but other extracolonic lesions have been reported only anecdotally.[2,6,12,16–18] It has been unclear whether the apparent scarcity of extraintestinal lesions is truly characteristic of the disease or reflects limited attempts so far to gather comprehensive phenotypic data. Moreover, there is likely to be a strong ascertainment bias toward colorectal polyposis and CRC because it is these phenotypes that usually lead to referral for *MUTYH* mutation analysis.

To date, no study has systematically evaluated extraintestinal manifestations in a large cohort of MAP patients. Nonetheless, knowledge of the natural course of a disease, including the true spectrum of manifestations and

Abbreviations used in this paper: CHRPE, congenital hypertrophy of the retinal pigment epithelium; CI, confidence interval; CRC, colorectal cancer; FAP, familial adenomatous polyposis; MAP, *MUTYH*-associated polyposis; SGA, sebaceous gland adenomas; SIR, standardized incidence ratios.

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clinopathological features, is important for differential diagnosis, adequate clinical surveillance of those at risk, and identification of the molecular pathways involved. To determine the spectrum and risk of extracolonic manifestations of MAP, and to overcome the limitations of small sample size, we conducted a retrospective collaborative study by pooling data from 3 research groups in the United Kingdom, the Netherlands, and Germany. Comprehensive clinical data were collected on 276 MAP patients with confirmed biallelic *MUTYH* mutations. Here we report the findings and suggest preliminary surveillance recommendations.

Materials and Methods

Patients and Sample Collection

Index patients had an adenomatous polyposis and were referred to 1 of 3 participating centers (Institute of Human Genetics, Bonn, Germany; Institute of Medical Genetics, Cardiff, UK; Centre for Human and Clinical Genetics, Leiden, The Netherlands) for mutation analysis of the *MUTYH* gene that was performed as described previously.[5,12,19] Index cases with biallelic *MUTYH* mutations (MAP patients) and their affected relatives were contacted and offered participation in the study. In addition, all available deceased siblings were included. Siblings were regarded as being affected only if medical records confirmed colorectal adenomatous polyposis or if biallelic germline *MUTYH* mutations were confirmed. Affected children and parents of index cases were included only if biallelic germline *MUTYH* mutations were identified. The study was approved by national and/or local ethics review boards at each center (the Multi-Centre Research Ethics Committee for Wales, ref. 06/MRE09/19, Medical Faculty of the University of Bonn ethics review board no. 063/04, and Leiden University Medical Centre ethics review board no. P01.019) and all patients enrolled in this study had given informed consent.

Genotyping/Nomenclature

To describe mutations we used the most up-to-date annotation for *MUTYH* (NM_001128425.1), which meant that numbering after nucleotide position c.157 (5′ end of exon 3; amino acid 53) is extended by 42 nucleotides (14 amino acids) compared to a previously used sequence (GenBank accession: U63329.1) and by 9 nucleotides compared to a previously introduced sequence (GenBank: NM_012222.1). This changes, for example, the description of the missense mutation c.494A>G; p.Tyr165Cys (Y165C) to c.536A>G;p.Tyr179Cys (Y179C) and c.1145G>A;p.Gly382Asp (G382D) to c.1187G>A; p.Gly396Asp (G396D).

Genotype-Phenotype Analysis

To examine potential genotype-phenotype correlations *MUTYH* genotypes were classified as described previously[15] to assess truncating vs nontruncating *MUTYH* mutations and alternative combinations of the 2 common *MUTYH* mutations G396D/Y179C. Separate analyses for biallelic combinations of mutations other than the G396D and Y179C were not done because the corresponding numbers of MAP patients were too small.

Phenotype/Data Collection

Information on medical and family histories was obtained during genetic counseling sessions and from medical records. A standardized inventory was used to ensure systematic evaluation of all potentially relevant disease manifestations. However, because of the different health care systems, ethics board decisions, and privacy policies, the procedures for gathering data differed between the centers. In the United Kingdom, information was gathered from regional genetics centers, hospital records, and by mailing a questionnaire to patients. In the Netherlands, this was supplemented by information obtained at telephone interview with MAP patients or their families in cases where there was unclear or incomplete data. In Germany, in addition to data collection by questionnaire and from medical records, a structured telephone interview was conducted with all index patients and affected relatives. Wherever possible, information provided by patients was confirmed from medical notes and histopathology records obtained from general practitioners, medical specialists, hospitals, and institutes. Multiple benign tumors of the same type in a patient were counted as 1 tumor. Seventeen cases were excluded from the study because there was insufficient clinical information (deceased long ago, lack of family contact, or untraceable medical records).

Statistical Analysis

Standardized incidence ratios (SIR) for different tumors were calculated by dividing observed numbers of cancers in the study cohort by the expected number in the general population. The expected number of cancers was calculated by multiplying the age- and gender-specific incidence rate in the general population with the corresponding cumulative observation time (person-years) in the study cohort. The age- and gender-specific incidence rates in the general population (years 2000–2004) were obtained from the population-based Cancer Registry of the Saarland, Germany, where multiple primary tumors and nonmelanoma skin cancers are routinely documented. Comparisons with the nation-specific incidence rates in the United Kingdom and the Netherlands did not show significant differences for relevant tumors such as duodenal, bladder, breast, ovarian, or endometrial cancer. In 1 patient, the age at diagnosis of ovarian cancer was unknown. To avoid over- or underestimation of risk, we used the mean age at diagnosis of ovarian cancer in the female general population (67 years of age), in this case, to enable estimation of the SIR for

Table 1. Baseline Data of the 3 Patient Groups

				Combined no. of patients		
	Germany	UK	Netherlands	Total	Index	Relatives
No. of patients	98	87	91	276	181	95
Gender ratio (*male/female*)	50/48	53/34	55/36	158/118	99/82	59/36
Age (*y*) at diagnosis, mean (range)	43 (24–68)	45 (12–65)	47 (21–70)	45 (12–70)	45 (12–68)	45 (27–70)
Age at evaluation, mean (range)	53 (28–84)	54 (17–78)	56 (32–83)	54 (17–84)	55 (17–84)	52 (19–82)
Mode of diagnosis (symptomatic/screening)	64/27	58/20	62/14	184/61	141/28	43/33
Deceased	8/98	19/87	30/91	57/276 (21)	29/181 (16)	28/95 (29)
Patients with extraintestinal lesions, n (%)	41/98 (42)	13/87 (15)	23/91 (25)	77/276 (28)	59/181 (33)	18/95 (19)
Patients with at least 1 extraintestinal malignancy, n (%)	18/98 (18)	4/87 (5)	13/91 (15)	35/276 (13)	26/181 (14)	9/95 (10)

ovarian cancer. The 95% confidence intervals of SIRs were calculated assuming that the numbers of observed cases followed a Poisson distribution. Cumulative age-dependent risks were calculated using the Kaplan–Meier method. Patients without cancer were censored at last observation or death, whichever occurred first. The log-rank test was used to compare cumulative risks between different genotypes. All reported *P* values are 2-sided. A P value $< .05$ was considered statistically significant. SPSS 15.0.1.1 (SPSS, Chicago, IL) was used for all analyses.

Results

Three-hundred and forty-six MAP patients with biallelic *MUTYH* mutations were approached and written consent was given by 293. Sufficient medical information could be obtained from 276 MAP patients (181 apparently unrelated index cases and 95 affected relatives) for inclusion in the study. The mutation spectrum and some phenotypic features of a subset of these patients have been described previously.[3,5,12,20] The characteristics of the patient groups from each participating country are summarized in Table 1. Detailed genetic and clinical information on all MAP patients included in this study is provided in Supplementary Table 1 and histological findings for all carcinomas identified more than once in the patient sample are listed in Supplementary Table 2.

The mean age at diagnosis of MAP was 45 years and the mean age at evaluation was 54 years. Most patients were diagnosed following symptomatic presentation. The male-to-female ratio was 1:3. The 3 national cohorts were similar in their size and characteristics, except for proportion of deceased patients, which ranged from <10% in the German cohort to approximately 30% in the Dutch cohort (Table 1). No significant differences in basic characteristics, such as mean age of diagnosis and mean age at evaluation, were identified between index-cases and their affected relatives (Table 1).

No correlations between genotype and age-dependent extracolonic tumor incidence were seen for either truncating vs nontruncating mutations or for different biallelic combinations of the mutations Y179C and G396D (data not shown).

Gastroduodenal Lesions

Of 150 patients who underwent esophagogastroduodenoscopy, 17 (11%) had gastric lesions (Table 2). In 4 of them (24%), gastric adenomas were described and 9 patients had fundic gland polyps only. Gastric cancer was observed 3 times; however, the incidence was not significantly increased compared to the general population (SIR: 4.2; 95% CI: 0.9–12) (Table 3). One patient with gastric cancer became symptomatic at 17 years of age, suggesting additional causative factors.

Duodenal polyposis occurred in 26 of 150 patients (17%) who underwent esophagogastroduodenoscopy. In 16 of these patients, adenomas were confirmed histologically, in 1 patient hyperplastic polyps were present, and in the remaining 9 patients the polyp type was unknown. Two duodenal carcinomas had been diagnosed at 56 and

Table 2. Gastroduodenal Findings

	Germany	UK	Netherlands	All patients	Median age at diagnosis (range)	FAP (reference)
Duodenoscopy conducted	80% (77/96)	45% (27/60)	51% (46/91)	61% (150/247)	—	—
Age (*y*) at duodenoscopy (range)	45 (24–69)	48 (14–48)	54 (28–70)	48 (14–70)	—	—
Duodenal polyps	19% (15/77)	7.5% (2/27)	20% (9/46)	17% (26/150)	48 (25–67)	50%–90%[24,25]
Duodenal cancer	—	—	4% (2/46)	1.3% (2/150)	61 (56–65)	3%–5%[24,25]
Gastric polyps	9% (7/77)	15% (4/27)	13% (6/46)	11% (17/150)	49 (17–67)	13%–84%[22,23]
Gastric cancer	2.6% (2/77)	3.7% (1/27)	—	2% (3/150)	38 (17–48)	<0.5%[27]
Esophagus carcinoma	1% (1/77)	—	2% (1/46)	1.5% (2/150)	53 (46–59)	—

FAP, familial adenomatous polyposis.

Table 3. Frequency of Extracolonic Cancers Observed More Than Once in 276 MAP Patients (158 Male, 118 Female)

Site of cancer	Gender	n	SIR (95% CI)	Obs %-risk by 75 y (95% CI)	Age (y) at diagnosis, median (range)
All extraintestinal malignancies[a]	Both	44	1.9 (1.4–2.5)	38 (23–52)	54 (27–78)
Esophagus	Both	2	5.5 (0.7–19.8)	2 (0–4)	53 (46–59)
Stomach	Both	3	4.2 (0.9–12.3)	1 (0–3)	38 (17–48)
Duodenum	Both	2	129 (15.7–465.9)	4 (0–9)	61 (56–65)
Bladder	Both	4	7.2 (2.0–18.4)	6 (0–12)	61 (45–67)
Skin[b]	Both	13	2.8 (1.5–4.8)	17 (4–29)	58 (30–71)
Lung	Both	2	0.6 (0.1–2.3)	3 (0–8)	60 (51–69)
Breast	F[c]	8	2.1 (0.9–4.2)	25 (0–51)	53 (45–76)
		11[d]	3.0 (1.5–5.3)		55 (45–78)
	M	1	53.5 (1.4–298)	1.5 (0–4.5)	56
Ovary[c]	F	3[e]	5.7 (1.2–16.7)	10 (0–22)	51 (45–56)
Endometrium[c]	F	2	4.6 (0.6–16.5)	3 (0–7)	51 (47–54)

CI, confidence interval; F, female; M, male; Obs%-Risk by 75 y, cumulative lifetime risk by 75 years in *MUTYH*-associated polyposis patients; SIR, standardized incidence ratio.

[a]Include also extraintestinal malignancies, which were observed only once.

[b]Include melanoma, spinous cell carcinoma, and basal cell carcinoma.

[c]Data related to female *MUTYH*-associated polyposis patients only.

[d]Related to affected females (n = 8) and total number of breast cancers (n = 11).

[e]Age of diagnosis was not known in 1 patient; for calculation mean age at diagnosis of ovarian cancer in the female general population (67 years of age) was used.

65 years of age, resulting in a high relative risk (SIR: 129; 95% CI: 16–466) (Table 3); the cumulative lifetime risk was calculated as 4%. No extraduodenal small-bowel cancer was found. In addition, carcinoid tumors were noted in 4 patients (2 located in the appendix, 2 in the small bowel).

Malignant Extraintestinal Tumors

Seventy-seven (28%) of the 276 MAP patients had at least 1 extraintestinal tumor. A total of 110 extraintestinal lesions was documented (including both synchronous and metachronous tumors), of which 44 (40%) were malignant. Thirty-five of the 276 MAP patients (13%) had at least 1 malignant extraintestinal lesion. The frequencies of both benign and malignant tumors differed between national cohorts (Table 1). Extraintestinal cancers had been diagnosed before presentation of colorectal MAP in 14 cases (12 index patients, 2 relatives) of the 35 patients (26 index cases, 9 relatives) with extraintestinal malignancies. The difference between index patients and relatives was not significant ($P = .26$). None of the 14 patients had a possible FAP-related extraintestinal tumor; all patients were referred for *MUTYH* mutation screening after the colorectal polyposis became apparent.

Compared to the general population, the incidence of extraintestinal malignancies as a whole was almost doubled in MAP patients (SIR: 1.9; 95% CI: 1.4–2.5) and lifetime risk was 38% (95% CI: 23%–52%) (Figure 1). The difference in tumor frequency between index patients and relatives was not significant ($P = .085$). Extraintestinal cancers reported at least 2 times in the whole patient sample included the 5 cancer types listed in Table 4*A*. A variety of other malignancies occurred only once (Supplementary Table 1). Eight female MAP patients had been affected by breast cancer at a median age of 55 years (Table 4). Notably, in 3 of them this cancer had occurred twice (bilateral synchronous, bilateral metachronous, and unilateral metachronous). In 1 of 3 females *BRCA1* and *BRCA2* germline mutation screening was performed with normal results. The incidence of breast cancer in females with MAP was significantly increased (SIR: 3.0; 95% CI: 1.5–5.3), but only if the number of cancers rather than the number of affected females was considered. Breast cancer was also diagnosed in 1 male MAP patient who tested negative for *BRCA1* and *BRCA2* germline mutations (SIR: 54; 95% CI: 1.4–298).

Skin cancers (melanomas, squamous epithelial carcinomas [spinaliomas, spinous cell carcinomas], and basal cell cancers) were the second most commonly reported cancers followed by bladder carcinomas (5% and 1.5% of patients, respectively) and their incidences were signifi-

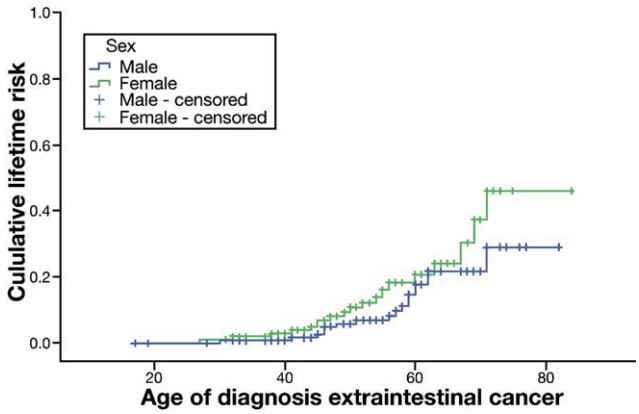

Figure 1. Cumulative lifetime risks for extraintestinal cancer in *MUTYH*-associated polyposis (MAP) patients.

Table 4. Extraintestinal Tumors

	Germany, % (*n*)	UK, % (*n*)	Netherlands, % (*n*)	All patients, % (*n*)	Median age at diagnosis (range)
(*A*) Malignancies					
Breast cancer[c]	6 (3/48)	3 (1/34 F)	11 (4/36 F)	7 (8/118 F)[a]	55 (45–78)[b]
Endometrial cancer[c]	4 (2/48)	—	—	1.7 (2/118 F)	51 (47–54)
Ovarian cancer[c]	4 (2/48)	3 (1/34 F)	—	2.5 (3/118 F)	51 (45–56)
Bladder carcinoma	2 (2/98)	—	2 (2/91)	1.5 (4/276)	61 (45–67)
Skin cancer	6 (6/98)	1 (1/87)	6.5 (6/91)	5 (13/276)	58 (30–71)
(*B*) Benign tumors	—	—	—	—	—
Benign skin tumors	12 (12/98)	7 (6/87)	13 (12/91)	11 (30/276)	50 (15–71)
Sebaceous gland adenoma/epithelioma	2 (2/98)	1.7 (2/87)	1 (1/91)	1.8 (5/276)	—
Epidermoid cysts/atheroma	3 (3/98)	—	1 (1/91)	1 (3/276)	—
Others[d]	8 (8/98)	5 (4/87)	11 (10/91)	8 (22/276)	—
Lipomas	7 (7/98)	1 (1/87)	—	3 (8/276)	37 (30–65)
Benign endometrial tumor[c]	6 (3/48)	—	2.7 (1/36)	3.4 (4/118 F)	43 (32–48)
Benign breast tumors[c]	4 (2/48)	3 (1/34 F)	2.7 (1/36)	3.5 (4/118 F)	43 (22–59)

[a]In 3 of 8 cases, a second metachronous or synchronous breast cancer occurred (F, female).
[b]All 11 breast cancers.
[c]All data related to female *MUTYH*-associated polyposis patients only.
[d]Fibrous histiocytoma, capillary hemangioma, pilar cyst, dermatofibroma, follicle cyst.

cantly increased (SIR: 2.8; 95% CI: 1.5–4.8 and SIR: 7.2; 95% CI: 2.0–18, respectively). As for breast cancer, the median ages at diagnosis of these cancers did not appear to be early (58 and 61 years, respectively).

Ovarian cancer was observed 3 times. Assuming an age at diagnosis of 67 years (the mean age at diagnosis of ovarian cancer in the female general population) in the 1 patient with unknown age at diagnosis, the risk was increased significantly (SIR: 5.7; 95% CI: 1.2–17). Endometrial cancer was noted in 2 patients, but the incidence was not increased significantly (Table 3). The present study may be underpowered to identify association of some cancers with MAP.

Benign Extraintestinal Lesions

No patients were identified with osteomas or desmoids. About half of the German and 7 Dutch patients were seen by an ophthalmologist (55 cases) and 3 (5.5%) of them were diagnosed with congenital hypertrophy of the retinal pigment epithelium (CHRPE), although we were unable to confirm whether the reported CHRPEs were of the type associated with FAP (multiple uni- or bilateral, sharp bordered, diffuse distributed lesions). At least 1 cystic lesion was found in 11 probands (jaw-bone cysts in 11 cases, hepatic cysts in 5 cases, and kidney cysts in 2 patients).

A variety of different benign cutaneous tumors were observed in 11% of patients (Table 4*B*). Interestingly, in 5 of the patients (1.8%), sebaceous gland adenomas (SGA) or sebaceous gland epitheliomas were reported (in 2 patients 1 SGA or sebaceous gland epitheliomas, in 2 patients 2 SGAs, and in 1 patient several SGAs). All 5 cases had a colorectal phenotype compatible with MAP (>20 to >100 adenomas), 4 patients had well-known pathogenic biallelic *MUTYH* mutations, and none of their families were suggestive of Lynch syndrome (Supplementary Table 1).

In the German cohort, subcutaneous lipomas were diagnosed in 7 patients; however, this finding was not confirmed by the other 2 groups. Benign "endometrial polyps" or endometrial hyperplasia was reported in several patients (Table 4*B*). In addition, a variety of other benign tumors were observed only once (Supplementary Table 1).

Discussion

Since its first description as an adenomatous colorectal polyposis in 2002, a number of extracolonic manifestations of MAP have been described.[2,5,6,12,16–18] However, many lesions have been reported sporadically and could suggest coincidence with limited clinical relevance. In this collaborative study involving 3 European centers, we undertook a comprehensive retrospective analysis of 276 MAP patients, the largest cohort to date, and assessed the incidence of both malignant and benign extracolonic lesions.

Upper Gastrointestinal Findings

We found gastric polyps in 11% and duodenal polyps in 17% of patients with MAP who had undergone upper gastrointestinal endoscopy, which is in accordance with previous findings in smaller studies.[2,21] It is unlikely that a substantial number of fundic gland polyps were caused by treatment with proton pump inhibitors because none of the patients were reported to suffer from gastroesophageal reflux, gastritis, or unspecific gastric symptoms. Thus, involvement of the upper gastrointestinal tract in MAP is not as common as in FAP, where gastric polyposis is present in approximately half of pa-

Table 5. Distribution of Duodenal Polyps

Site of duodenal polyps	No. of patients[a]
Total	24
Bulbus duodeni	5
Periampullary region	4
Duodenum descendens[b]	6
Flexura duodeni inferior	3
Site unknown	11

[a]Some patients are listed more than once depending on the distribution of duodenal polyps.
[b]Outside periampullary region.

tients (range, 13%–84%)[22,23] and duodenal polyposis in 50%–90%.[24,25] However, the gastric polyps in MAP cases included a number that were reported to be adenomas (although the histology could not be verified by independent review) and gastric cancers were noted in 3 patients. Our preliminary observations are based on small numbers, but the previously reported identification of biallelic somatic *MUTYH* mutations in sporadic gastric cancer[26] suggests that defects in the base excision repair pathway may be relevant in development of some gastric cancers.

The distribution and relative frequency of duodenal polyps was comparable to FAP[25,27]; however, the numbers were small (Table 5). Although duodenal polyps were found to be less frequent in MAP (17%) than is reported in FAP, the increase in relative risk (SIR: 129) and the lifetime risk of duodenal cancer (around 4%) appeared similar.[25,28,29] Recently, 2 additional cases of advanced duodenal carcinoma were reported in MAP patients.[18] It is noteworthy that development of duodenal cancer in MAP in the absence of obvious duodenal polyposis has been observed,[20] indicating that screening strategies that have been developed for patients with FAP may not be appropriate or adequate in MAP.

Extraintestinal Cancers

Extraintestinal malignancies were diagnosed in 35 of 276 MAP patients (13%). Compared to the general population, the incidence was almost doubled (SIR: 1.9) and the cumulative lifetime risk was approximately 38%. A characteristic feature of the extraintestinal malignancies that were observed more than once was their relatively advanced age at diagnosis (median 51–61 years; range, 30–78 years).

The risk of bladder cancer in MAP was similar to the risk of urinary tract cancers in Lynch syndrome.[30–33] However, in contrast to Lynch syndrome, no cancers were located in the upper part of the urinary tract (renal pelvis, ureter), and the MAP-associated cancers included 1 squamous cell carcinoma in addition to urothelial cancers.

A single thyroid carcinoma occurred in the cohort, and only 1 additional case in a patient with MAP has been reported in the literature.[16] The 2 cancers were of different histological types. Thus, there does not appear to be a significant association of thyroid cancer with MAP, in contrast to the established association with FAP.

A trend toward an increased risk for breast cancer and gynecological cancers (endometrial cancer and ovarian cancer) was seen in our data and has also been suggested by others. A significant increase in breast cancer was reported previously in the Dutch subgroup of our cohort.[12] Breast tumors have also been reported in *MUTYH* knockout mice,[34] and the *BRCA* genes are involved in base excision repair of 8-oxo-G lesions,[35] suggesting a mechanistic basis for a phenotypic association. The high frequency of metachronous or synchronous breast cancer in our cohort was striking, and the number of cancers observed in female MAP patients was increased significantly. Nonetheless, breast cancer is very rarely associated with MAP because no biallelic carriers of the 2 common *MUTYH* mutations were found among 691 breast cancer patients.[36] In contrast to hereditary breast and ovarian cancer, breast cancer in MAP patients was a late onset manifestation occurring between the 5th and 8th decades of life.

The occurrence of 3 MAP patients with ovarian and 2 with endometrial cancer in our cohort was conspicuous. Systematic screening for *MUTYH* mutations has been undertaken in 225 endometrial cancer patients and 1 biallelic mutation carrier was identified.[37] Recently, 2 additional MAP patients with endometrial cancer were reported,[38] and we have identified another in an MAP patient who was not included in this study.

Benign Extraintestinal Lesions

FAP-associated extraintestinal lesions were not prevalent in MAP patients. Importantly, no osteomas or desmoids were reported in any of the 276 patients in the present study and epidermoid cysts were seen rarely. CHRPE was diagnosed in only 3 patients, and it is questionable whether or not the specific type characteristic of classical FAP was seen. Given the rarity of CHRPE in our cohort and the literature on MAP, the presence of retinal pigment anomalies in the general population, and taking into account the subjective diagnosis by inexperienced ophthalmologists,[39] there is no evidence for an association between MAP and CHRPE. It has been reported that the presence of osteomas, CHRPE, and desmoids give a high probability of detecting an *APC* germline mutation[40]; our data suggest that osteomas and desmoids are valuable markers that differentiate between (attenuated) FAP and MAP.

Benign cutaneous tumors were reported frequently (11%) in our MAP cohort. Reliable population-based figures are not available for comparison, but the identification of 5 cases with sebaceous gland tumors was striking. Such tumors (sebaceous gland adenomas, epitheliomas, and carcinomas) are extremely rare in the general population, but are recognized as marker tumors for Muir–Torre syndrome, a variant of Lynch syndrome.[41–44] Three

case reports have also described sebaceous gland tumors in MAP patients with proved biallelic *MUTYH* mutations (in 1 patient together with an endometrial carcinoma),[16,37,45] supporting the notion that the association of these tumors with colorectal tumors is not restricted to patients with germline mutations of the mismatch-repair genes. Thus, similar to Lynch syndrome, sebaceous gland tumors might serve as a marker lesion that allows a presymptomatic diagnosis of MAP in a subset of patients. In contrast to Muir–Torre syndrome, sebaceous gland tumors in MAP patients are microsatellite stable with normal expression of mismatch-repair genes.[16] Recently, it was noticed that up to one-third of Muir–Torre patients had microsatellite stable tumors[43]; as a consequence, the authors stated that there must be at least 1 other variant of Muir–Torre syndrome with different molecular genetic mechanisms.

The high incidence of lipomas (3 cases occurred within a sibship) in the German subgroup might be due to chance or underreporting in the Dutch and UK subgroups, or represent a rare potential MAP manifestation similar to other specific lesions reported in single families only, eg, pilomatrixomas (pilomatricomas) in 3 siblings.[17] Lipomas occurred in 3 of 93 *APC* mutation–positive Swiss FAP patients[46]; multiple pilomatrixomas were also described in patients with FAP[47,48] and also appear to be associated with a variety of hereditary disorders rather than only adenomatous polyposis syndromes.[49]

Phenotypic and Mechanistic Overlap Between MAP and Lynch Syndrome?

The occurrence of Lynch syndrome–associated tumors in MAP (sebaceous gland tumors, colorectal, endometrial, and ovarian cancers) may reflect shared aspects of pathophysiology. Both the mismatch-repair and the base-excision-repair pathway are involved in the removal of oxidative DNA damage, partly in different ways, partly in a synergistic manner.[50,51] In particular, the MSH2/MSH6 protein complex seems to be relevant for a physical and functional cooperation between the pathways by enhancing the substrate recognition, binding affinity, and glycosylase activity of the MUTYH enzyme,[52] and in mismatch-repair–deficient cells the repair of oxidative damage is impaired and 8-oxoG is increased.[53]

Ascertainment Bias

Retrospective studies like the present one are prone to various sources of bias and it is impossible to eliminate all of them. The patient groups from the 3 centers and the index patients vs relatives were very similar in terms of size, gender ratio, age at diagnosis, and age at evaluation. The high number of deceased patients in the Dutch cohort can be explained partly by the inclusion of relatively older patients and the better access to this group in the Dutch registry. The frequency of documented extracolonic lesions differed between the centers. The lower incidence of gastroduodenal tumors in the UK cohort might be caused by chance because the number of patients who underwent gastroduodenoscopy was low. The differences in incidence of extraintestinal lesions could also reflect the different methods of data gathering that were used by the centers because of their different health care systems and privacy and research ethics policies. The telephone interview conducted with every German patient and in half of the Dutch patients proved to be a very sensitive method to collect medical information and may explain their apparently higher tumor incidence. Therefore, a slight underestimation of the extracolonic tumor incidence in the sample as a whole cannot be excluded. Conversely, an overestimation of cancer risk could have been made because the more intensive medical follow-up of MAP patients than individuals from the general population might increase detection of tumors.[54]

No strong ascertainment bias toward or against extracolonic tumors is expected in MAP index patients because the presence of an adenomatous polyposis is the selection criterion for initiating *MUTYH* screening. None of the MAP index patients were referred for mutation analysis in polyposis genes because of extraintestinal tumors; *MUTYH* screening was performed routinely in patients with an adenomatous polyposis (>20 adenomas) irrespective of the severity of colorectal disease. There were no known selection criteria regarding recruitment of at-risk relatives. Frequency of extraintestinal cancer did not differ significantly between index cases and relatives. However, patients who died early due to an extraintestinal malignancy before colorectal polyposis became apparent would escape inclusion in a systematic MAP study such as the present one, and this could lead to a relative underestimation of the risk of early onset cancers with a poor prognosis. Indeed, in 14 of 35 patients with extracolonic malignancies (40%), the extracolonic cancer manifested before (by 2–15 years) the diagnosis of polyposis was made.

In accordance with studies on other hereditary tumor syndromes,[30,54,55] some extracolonic cancers that are observed frequently in the general population, such as lung cancer, prostate cancer, and leukemia, were comparatively infrequent in our series. Mostly, the low frequency can be attributed to mean age at last observation of the patients, which was before the age by which the majority of the late-onset sporadic cancers occurs in the general population.

Surveillance

Based upon the attenuated or atypical FAP-like colorectal phenotype in the vast majority of MAP patients, it has been suggested by a European expert panel that the surveillance protocol applied in attenuated FAP is appropriate for MAP patients.[56] This protocol includes complete colonoscopy at biannual intervals starting from

18 to 20 years and gastroduodenoscopy starting at between 25 and 30 years of age. Our findings support these recommendations for gastrointestinal surveillance in MAP, although recent genotype-phenotype correlation might enable refinement of these protocols in the future.[15]

Although the overall incidence of extraintestinal cancers was almost doubled in MAP patients, no predominant tumor type or marked shift toward early onset was observed, suggesting that extraintestinal tumor surveillance is unlikely to offer great benefit. The borderline increase in the risk of (late onset) breast cancer should be addressed adequately by existing surveillance protocols that are offered to females in the general population in most Western countries.[57–59] The risk of endometrial cancer was not increased significantly and current screening modalities for ovarian and endometrial cancers are of limited or uncertain value.[30,60] In Lynch syndrome, most surveillance protocols no longer include screening for urinary tract tumors by urine cytology because of the low sensitivity and high number of false-positive results.[33,61] As with other tumor predisposition syndromes associated with a variety of different rare tumors, MAP patients and their clinicians should be sensitive to suspicious or unusual symptoms and be aware of the overall increase in cancer incidence.

Conclusions

We evaluated the spectrum and incidence of gastroduodenal and extraintestinal tumors in the largest cohort of MAP patients examined so far. Although no predominant cancer was apparent, the overall incidence of extraintestinal malignancies was increased. The tumor spectrum associated with MAP is wider than previously recognized and there are phenotypic overlaps with Lynch syndrome. No genotype-phenotype correlation was found for extracolonic lesions. The presence of osteomas or desmoids in a patient with polyposis points strongly to a diagnosis of FAP rather than MAP, while the presence of sebaceous gland tumors is a characteristic of a subgroup of patients with either MAP or Lynch syndrome.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2009.08.052.

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Databases: OMIM 608456 (MAP); *Human Gene Mutation Database (HGMD):* http://uwcmml1s.uwcm.ac.uk/uwcm/mg/search/9315115.html; *MUTYH* Leiden Open Variation Database (LOVD): http://chromium.liacs.nl/LOVD2/colon_cancer/home.php.

Conflicts of interest

The authors disclose no conflicts.

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Supplementary Table 1. Intestinal and Extraintestinal Tumor Spectrum, *MUTYH* Mutations and Cause of Death in 276 *MUTYH*-Associated Polyposis Patients

Patient no.	Index case (1)/relative	Center	Gender	Mutation 1	Mutation 2	Age[a] at diagnosis	Cause and age[a] at death	Maximal polyp number colorectum	Colorectal cancer (age[a])	Gastroduodenoscopy (age[a])	No. and histology of duodenal polyposis	Duodenal cancer	No. and type of gastric polyps	Extracolonic tumor (age[a] at diagnosis)
10	1	B	M	c.749G>A; p.Gly250Asp	c.1147delC; p.Ala385ProfsX25	37	alive	multiple	Yes (50)	yes	no	no	none	
10	2	B	M	c.749G>A; p.Gly250Asp	c.1147delC; p.Ala385ProfsX25	43	alive	unknown	no	yes	unknown	no	unknown	melanoma (59)
26	1	B	F	c.536A>G; p.Tyr179Cys	c.1437_1499delGGA; p.Glu480del	29	alive	multiple	yes (29)	yes (37)	no	no	none	
26	2	B	F	c.536A>G; p.Tyr179Cys	c.1437_1499delGGA; p.Glu480del	33	alive	250	yes (33)	yes (36)	1 adenoma	no	none	lipoma (30), 2 other benign tumors (33), dermoid cyst (33), hepatic cysts
26	3	B	F	c.536A>G; p.Tyr179Cys	c.1437_1499delGGA; p.Glu480del	33	alive	50	no	yes (45)	no	no	none	lipoma
94	1	B	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	68	alive	>100	no	no	unknown	unknown	unknown	
370	1	B	F	c.536A>G; p.Tyr179Cys	c.1147delC; p.Ala385ProfsX25	29	alive	>50	no	yes (41)	1 adenoma	no	none	benign skin tumor (15), maxillary cysts (21)
395	1	B	M	c.1187G>A; p.Gly396Asp	c.1214C>T; p.Pro405Leu	34	alive	unknown	no	yes (49)	no	no	none	benign skin tumor (50), spinalioma (60)
398	1	B	F	c.536A>G; p.Tyr179Cys	c.734G>A; p.Arg245His	43	alive	500–1000	yes (44)	yes (44)	few polyps, histology unknown	no	none	
415	1	B	M	c.504+19_31del13	c.734G>A; p.Arg245His	53	alive	>100	yes (49)	yes	no	no	none	
489	1	B	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	36	alive	100–500	no	yes (49)	no	no	1 polyp, histology unknown	lipoma (54), ovarian cancer (56), benign skin tumor (56)
489	2	B	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	45	alive	100	yes (46)	yes (45)	no	no	none	lipoma (37), hepatic cysts (48)
526	1	B	F	c.536A>G; p.Tyr179Cys	c.933+3A>C	41	alive	50–100	yes (41)	yes (41)	yes	no	none	bladder carcinoma (45)
526	2	B	F	c.536A>G; p.Tyr179Cys	c.933+3A>C	27	alive	<50	yes (38)	yes (25)	2 adenomas	no	none	jaw-bone cysts (10)
548	1	B	M	c.734G>A; p.Arg245His	c.1147delC; p.Ala385ProfsX25	36	gastric cancer (41)	100–200	no	yes (32)	no	no	none	gastric cancer (38)
620	1	B	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	60	alive	>100	yes (60)	yes (60)	no	no	none	
641	1	B	F	c.536A>G; p.Tyr179Cys	c.1147delC; p.Ala385ProfsX25	31	alive	70	no	yes (31)	no	no	none	maxillary cysts (23), benign breast tumor (31)
659	1	B	M	c.536A>G; p.Tyr179Cys	c.933+3A>C	52	alive	100–500	yes (52)	yes (52)	no	no	none	
660	1	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	46	alive	50	yes (46)	yes (46)	no	no	1 polyp, histology unknown	
660	2	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	45	alive	>50	no	yes (24)	no	no	none	
660	4	B	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	41	alive	multiple	no	no	unknown	unknown	unknown	
660	5	B	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	43	CRC (43)	multiple	yes (43)	no	unknown	unknown	unknown	
676	1	B	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	38	unknown (52)	30–40	no	yes (46)	no	no	none	esophagic cancer (46)
698	1	B	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	49	alive	multiple	yes (49)	yes (53)	no	no	none	
719	1	B	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	47	alive	150	yes (47)	yes (47)	1 adenoma	no	few fundic gland polyps	hepatic cysts (47)
757	1	B	F	c.536A>G; p.Tyr179Cys	c.933+3A>C	40	alive	50–100	no	yes (40)	no	no	none	jaw-bone cysts (14)
760	1	B	F	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	57	alive	5	yes (57)	yes (61)	no	no	none	
774	1	B	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	48	alive	>40	no	no	unknown	unknown	unknown	
786	1	B	F	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	39	alive	30	no	yes (39)	no	no	none	
787	1	B	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	51	alive	100–500	no	yes (56)	4 polyps, histology unknown	no	none	breast cancer (56)

Supplementary Table 1. (Continued)

Patient no.	Index case (1)/relative	Center	Gender	Mutation 1	Mutation 2	Age[a] at diagnosis	Cause and age[a] at death	Maximal polyp number colorectum	Colorectal cancer (age[a])	Gastroduodenoscopy (age[a])	No. and histology of duodenal polyposis	Duodenal cancer	No. and type of gastric polyps	Extracolonic tumor (age[a] at diagnosis)
818	1	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	37	alive	>100	no	yes (37)	no	no	none	
818	2	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	35	alive	multiple	no	yes (40)	1 adenoma	no	none	
826	1	B	F	c.536A>G; p.Tyr179Cys	c.933+3A>C	28	alive	multiple	no	yes (35)	1 adenoma	no	3 adenomas	adenoma small bowel (49)
826	7	B	F	c.536A>G; p.Tyr179Cys	c.933+3A>C	31	alive	40	yes (31)	yes	no	no	none	
848	1	B	F	c.1147delC; p.Ala385ProfsX25	c.1437_1499delGGA; p.Glu480del	38	alive	100–500	yes (38)	yes (60)	>15 adenomas	no	none	lipoma (65)
858	1	B	M	c.536A>G; p.Tyr179Cys	c.824-829dupCAGGAG; p.Gly276_Gly277insAla,Gly	49	alive	>150	yes (49)	yes (49)	no	no	none	bladder carcinoma (62), basalioma (62)
872	1	B	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	36	alive	50–100	no	yes (37)	3 adenomas	no	none	
885	1	B	F	c.470C>T; p.Pro157Leu	c.1187G>A; p.Gly396Asp	36	alive	<100	yes (46)	yes (46)	no	no	none	melanoma (32)
914	1	B	M	c.289C>T; p.Arg97X	c.1214C>T; p.Pro405Leu	51	alive	unknown	yes (51)	yes (51)	no	no	none	testicular cancer (41)
925	1	B	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	48	CRC (51)	36	yes (48)	yes (48)	many adenomas	no	none	benign skin tumor (15)
973	1	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	50	alive	21–50	no	yes (54)	no	no	none	
973	2	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	43	alive	21–50	yes (43)	no	unknown	unknown	unknown	
982	1	B	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	39	alive	multiple	yes (54)	yes (54)	no	no	none	
994	1	B	F	c.884C>T; p.Pro295Leu	c.1437_1499delGGA; p.Glu480del	39	alive	20–30	yes (39)	no	unknown	unknown	unknown	
1062	1	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	48	alive	500–1000	yes (48)	yes (49)	no	no	none	
1065	1	B	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	42	alive	unknown	yes (42)	yes (50)	no	no	none	benign skin tumor (36), benign endometrial tumor (48)
1065	2	B	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	28	alive	50–100	no	yes (28)	no	no	none	
1068	1	B	F	c.820C>T; p.Arg274Trp	c.1518+2T>C	60	alive	unknown	no	yes (55)	no	no	none	
1077	1	B	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	44	alive	50–100	no	no	unknown	unknown	unknown	
1077	2	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	61	alive	>60	yes (64)	no	unknown	unknown	unknown	hepatic cysts (70)
1083	1	B	M	c.536A>G; p.Tyr179Cys	c.1012C>T; p.Gln338X	24	alive	50–100	no	yes (25)	no	no	none	
1087	1	B	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	54	CRC (55)	>100	yes (54)	yes (54)	no	no	none	b-cell lymphoma (46)
1111	1	B	M	c.536A>G; p.Tyr179Cys	c.1171C>T; p.Gln391X	49	alive	50–70	no	yes (44)	unknown number of adenomas	no	6 fundic gland polyps	
1111	4	B	M	c.536A>G; p.Tyr179Cys	c.1171C>T; p.Gln391X	42	alive	100	yes (43)	yes (52)	no	no	none	basalioma (48, 51, 53)
1114	1	B	F	c.734G>A; p.Arg245His	c.1147delC; p.Ala385ProfsX25	63	alive	500–1000	yes (68)	no	unknown	unknown	unknown	gangliocystoma (52)
1114	2	B	F	c.734G>A; p.Arg245His	c.1147delC; p.Ala385ProfsX25	66	CRC (68)	unknown	yes (66)	no	unknown	unknown	unknown	
1114	3	B	M	c.734G>A; p.Arg245His	c.1147delC; p.Ala385ProfsX25		CRC (63)	unknown	yes (63)	unknown				
1125	1	B	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	30	alive	6–10	yes (30)	yes (51)	2 adenomas	no	none	benign breast tumor (59)
1126	1	B	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	38	alive	>100	yes (38)	yes (38)	no	no	fundic gland polyp	
1175	1	B	F	c.536A>G; p.Tyr179Cys	c.734G>A; p.Arg245His	36	alive	80	no	yes (36)	no	no	none	
1175	2	B	F	c.536A>G; p.Tyr179Cys	c.734G>A; p.Arg245His	40	alive	<100	no	yes (40)	no	no	1 adenoma, 2 fundic gland polyps	benign skin tumor (36)
1180	1	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	35	alive	<100	yes (47)	yes (47)	no	no	none	sebaceous gland epithelioma (51)
1211	1	B	F	c.1147delC; p.Ala385ProfsX25	c.1187G>A; p.Gly396Asp	37	alive	>50	yes (37)	yes (61)	no	no	none	
1222	1	B	M	c.734G>A; p.Arg245His	c.1187G>A; p.Gly396Asp	52	alive	70	yes (52)	yes (53)	no	no	none	sebaceous gland adenoma (47), other benign tumors (48)
1229	1	B	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	63	alive	>50	yes (63)	no	unknown	unknown	unknown	kidney and hepatic (64)
1241	1	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	52	alive	6–10	no	no	unknown	unknown	unknown	

Supplementary Table 1. (Continued)

Patient no.	Index case (1)/relative	Center	Gender	Mutation 1	Mutation 2	Age[a] at diagnosis	Cause and age[a] at death	Maximal polyp number colorectum	Colorectal cancer (age[a])	Gastroduodenoscopy (age[a])	No. and histology of duodenal polyposis	Duodenal cancer	No. and type of gastric polyps	Extracolonic tumor (age[a] at diagnosis)
1241	2	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	53	alive	>150	no	yes (53)	no	no	none	pancoast tumor (51)
1257	1	B	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	48	alive	100–500	yes (48)	yes (47)	no	no	fundic gland polyp	
1258	1	B	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	49	alive	50–100	yes (49)	yes (49)	no	no	none	
1260	1	B	F	c.628C>T; p.Gln210X	c.1147delC; p.Ala385ProfsX25	44	alive	<50	no	yes (48)	2 polyps, histology unknown	no	none	
1286	1	B	F	c.536A>G; p.Tyr179Cys	c.1214C>T; p.Pro405Leu	39	alive	30	no	no	unknown	unknown	unknown	
1286	2	B	M	c.536A>G; p.Tyr179Cys	c.1214C>T; p.Pro405Leu	44	alive	many	no	yes (51)	no	no	none	
1293	1	B	F	c.536A>G; p.Tyr179Cys	c.933+3A>C	45	CRC (52)	multiple	yes (45)	yes (45)	no	no	none	thyroid cancer (38), breast cancer (45), gastric cancer (48)
1309	1	B	M	c.463-1G>C	c.1147delC; p.Ala385ProfsX25	32	alive	75	no	yes (32)	no	no	none	lipoma (33)
1309	2	B	F	c.463-1G>C	c.1147delC; p.Ala385ProfsX25	37	alive	>25	no	yes (37)	no	no	none	
1309	3	B	M	c.463-1G>C	c.1147delC; p.Ala385ProfsX25	36	alive	50–100	no	yes (36)	no	no	none	
1315	1	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	66	alive	>200	yes (66)	yes (69)	no	no	none	
1323	1	B	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	33	alive	few	no	yes (35)	no	no	none	endometrial carcinoma (54), benign skin tumor
1334	1	B	F	c.643G>A; p.Val215Met	c.884C>T; p.Pro295Leu	30	alive	multiple	yes (30)	yes (30)	multiple adenomas	no	none	
1338	1	B	M	c.884C>T; p.Pro295Leu	c.884C>T; p.Pro295Leu	36	alive	50–100	no	yes (41)	no	no	none	
1358	1	B	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	40	alive	51	yes (48)	yes (49)	no	no	none	breast cancer (49)
1358	2	B	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	45	alive	<40	yes (53)	yes (45)	no	no	none	
1371	1	B	F	c.536A>G; p.Tyr179Cys	c.1147delC; p.Ala385ProfsX25	37	alive	multiple	no	yes (37)	no	no	none	
1372	1	B	M	c.1437_1499delGGA; p.Glu480del	c.1437_1499delGGA; p.Glu480del	37	alive	multiple	yes (37)	yes (37)	no	no	none	
1389	1	B	M	c.55C>T; p.Arg19X	c.1147delC; p.Ala385ProfsX25	43	alive	60–70	yes (43)	yes (44)	no	no	none	
1406	1	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	53	alive	>100	yes (53)	no	unknown	unknown	unknown	
1406	2	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	55	alive	50–100	no	yes (55)	no	no	none	
1412	1	B	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	44	alive	numerous	yes (44)	yes (50)	no	no	none	lipoma
1412	2	B	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	34	alive	<5	no	unknown				endometrial carcinoma (47)
1412	3	B	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	33	alive		yes (33)	no	unknown	unknown	unknown	benign endometrial tumor (32), ovarian cancer (45)
1421	1	B	M	c.536A>G; p.Tyr179Cys	c.933+3A>C	52	alive		no	no	unknown	unknown	unknown	benign skin tumor (25)
1451	1	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	49	alive	some	yes (49)	no	unknown	unknown	unknown	testical teratoma (28)
1451	2	B	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	44	alive	26	yes (44)	no	unknown	unknown	unknown	benign endometrial tumor (48)
561	1	B	F	c.722G>A; p. Arg241Gln	c.1187G>A; p.Gly396Asp	45	alive	100–500	yes (45)	yes (69)	no	no	none	breast cancer (60, 68), spinalioma (68), benign skin tumor
1434	1	B	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	52	alive	50–60	no	no	unknown	unknown	unknown	
1401	1	B	F	c.536A>G; p.Tyr179Cys	c.884C>T; p.Pro295Leu	31	alive	50–60	yes (31)	yes (31)	no	no	none	
1468	1	B	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	58	alive		yes (64)	yes (50)	unknown number of hyperplastic polyps	no	unknown number and histology	

Supplementary Table 1. (Continued)

Patient no.	Index case (1)/relative	Center	Gender	Mutation 1	Mutation 2	Age[a] at diagnosis	Cause and age[a] at death	Maximal polyp number colorectum	Colorectal cancer (age[a])	Gastroduodenoscopy (age[a])	No. and histology of duodenal polyposis	Duodenal cancer	No. and type of gastric polyps	Extracolonic tumor (age[a] at diagnosis)
1512	1	B	M	c.536A>G; p.Tyr179Cys	c.933+3A>C	40	alive	multiple	no	yes (40)	no	no	none	
2220	1	L	F	c.1214C>T; p.Pro405Leu	c.1214C>T; p.Pro405Leu		alive		no	no	unknown	unknown	unknown	
2380	1	L	M	c.1214C>T; p.Pro405Leu	c.739 C>T; p.Arg247X	48	alive	10–100	yes (48)	yes (47)	no	no	none	
19036	1	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	41	CRC (44)	multiple	yes (41)	no	unknown	unknown	unknown	
19045	1	L	F	c.536A>G; p.Tyr179Cys	c.691-1 G>A	42	alive	10–50	no	no	unknown	unknown	unknown	
19047	1	L	F	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	33	alive	10–20	no	no	unknown	unknown	unknown	
19047	1	L	F	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	40	alive	polyposis	no	yes (60)	no	no	none	
19047	2	L	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	30	alive	1	no	no	unknown	unknown	unknown	
19047	3	L	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	38	alive	2	no	no	unknown	unknown	unknown	
19047	4	L	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	57	CRC (58)	polyps	yes (57)	no	unknown	unknown	unknown	
19047	5	L	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	70	alive	polyposis	yes (70)	no	unknown	unknown	unknown	
19049	1	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	46	alive	multiple	no	no	unknown	unknown	unknown	bladder carcinoma (60), other benign tumors (62), benign skin tumor
19049	2	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	53	unknown (71)	100–1000	yes (53)	no	unknown	unknown	unknown	
19049	3	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	56	other cancer than CRC (74)	100–1000	yes (56)	yes (57)	no	no	none	carcinoma of the larynx (48), benign skin tumor (60), bladder carcinoma (67)
19049	4	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	50	accident (77)	100–1000	no	no	unknown	unknown	unknown	prostate cancer (62), benign skin tumor (63)
19053	1	L	M	c.536A>G; p.Tyr179Cys	c.933+3A>C	51	alive	polyposis	yes (51)	no	unknown	unknown	unknown	
19053	2	L	M	c.536A>G; p.Tyr179Cys	c.933+3A>C	53	disease other than cancer (76)	polyposis	yes (53)	no	unknown	unknown	unknown	
19095	1	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	36	alive	>100	no	no	unknown	unknown	unknown	
19095	2	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	37	alive	3	no	yes (52)	unknown numberof adenomas	no	none	
19095	3	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	44	alive	25–50	no	yes (61)	no	no	none	
19095	4	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	46	alive	numerous	no	yes (50)	no	no	fundic gland polyp	
19106	1	L	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	40	alive	10–50	yes (40)	yes (50)	25 adenomas	no	fundic gland polyp	
19221	1	L	M	c.536A>G; p.Tyr179Cys	c.1214C>T; p.Pro405Leu	45	CRC (56)	30–100	yes (45)	yes (56)	1 adenoma	yes	none	melanoma (30)
19221	2	L	F	c.536A>G; p.Tyr179Cys	c.1214C>T; p.Pro405Leu	46	CRC (46)	unknown	yes (46)	no	unknown	unknown	unknown	
19247	1	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	43	CRC (64)	multiple	yes (43)	yes (63)	no	no	none	benign skin tumor
19247	2	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	51	CRC (51)	unknown	yes (51)	no	unknown	unknown	unknown	
19247	3	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	47	unknown (52)	60	no	no	unknown	unknown	unknown	
20090	1	L	M	c.536A>G; p.Tyr179Cys	c.1214C>T; p.Pro405Leu	0	alive	10–100	yes (50)	yes (62)	no	no	none	
20090	2	L	M	c.536A>G; p.Tyr179Cys	c.1214C>T; p.Pro405Leu	39	CRC (40)	few	yes (39)	no	unknown	unknown	unknown	
50176	1	L	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	52	alive	50	no	yes (52)	no	no	none	
50176	2	L	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	48	alive	7	no	yes (51)	no	no	none	
51063	1	L	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	33	alive	50–100	yes (44)	yes (46)	no	no	20 fundic gland polyps	benign skin tumor (46)
51545	1	L	M	c.536A>G; p.Tyr179Cys	c.1147delC; p.Ala385ProfsX25	42	alive	polyposis	no	yes (61)	no	no	none	

Supplementary Table 1. (Continued)

Patient no.	Index case (1)/relative	Center	Gender	Mutation 1	Mutation 2	Age[a] at diagnosis	Cause and age[a] at death	Maximal polyp number coloreclum	Colorectal cancer (age[a])	Gastroduodenoscopy (age[a])	No. and histology of duodenal polyposis	Duodenal cancer	No. and type of gastric polyps	Extracolonic tumor (age[a] at diagnosis)
52105	1	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	43	alive	polyposis	no	yes (68)	1 adenoma	no	none	basalioma (71)
52105	1	L	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	33	alive	10–20	no	yes (50)	no	no	none	
52240	1	L	F	c.1214C>T; p.Pro405Leu	c.1214C>T; p.Pro405Leu	57	CRC (58)	polyposis	yes (58)	no	unknown	unknown	unknown	breast cancer (55)
52596	1	L	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	39	alive	50–100	yes (39)	yes (42)	no	no	none	
52638	1	L	M	c.1187G>A; p.Gly396Asp	c.325C>T; p.Arg109Trp	52	CRC (53)	50–100	yes (52)	yes (50)	no	no	none	benign skin tumor (50)
52654	1	L	M	c.1214C>T; p.Pro405Leu	c.1214C>T; p.Pro405Leu	37	CRC (39)	100–1000	yes (37)	no	unknown	unknown	unknown	
52654	2	L	F	c.1214C>T; p.Pro405Leu	c.1214C>T; p.Pro405Leu	41	CRC (42)	numerous	yes (41)	no	unknown	unknown	unknown	
52689	1	L	M	c.1171C>T; p.Gln391X	c.1171delC; p.Gln391X	36	unknown cause/ age	110–120	no	no	unknown	unknown	unknown	
52699	1	L	M	c.536A>G; p.Tyr179Cys	c.1147delC; p.Ala385ProfsX25	37	alive	10–100	no	yes (37)	no	no	none	
53029	1	L	F	c.536A>G; p.Tyr179Cys	c.1214C>T; p.Pro405Leu	44	alive	10–100	no	yes (59)	no	no	1fundic gland polyp	
53029	2	L	M	c.536A>G; p.Tyr179Cys	c.1214C>T; p.Pro405Leu	41	CRC (46)	multiple	yes (41)	yes (42)	no	no	none	
53231	1	L	F	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	59	CRC (62)	polyposis	yes (59)	no	unknown	unknown	unknown	
53276	1	L	M	c.1187G>A; p.Gly396Asp	c.1214C>T; p.Pro405Leu	48	alive	100–1000	yes (48)	yes (57)	yes	no	none	basalioma (58)
54092	1	L	F	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	60	alive	<100	yes (60)	no	unknown	unknown	unknown	
54092	2	L	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	57	alive	30-50	no	no	unknown	unknown	unknown	
54140	1	L	F	c.1227_1228dupGG; p.Glu410fs43	c.1227_1228dupGG; p.Glu410fs43	42	alive	10–50	yes (42)	no	unknown	unknown	unknown	cervix carcinoma (27), breast cancer (50)
54178	1	L	F	c.1187G>A; p.Gly396Asp	c.1214C>T; p.Pro405Leu	44	alive	50–100	yes (44)	yes (52)	no	no	none	
54186	1	L	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	45	CRC (49)	polyposis	yes (45)	no	unknown	unknown	unknown	basalioma (41)
54186	2	L	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	43	CRC, (44)	50	yes (43)	yes (43)	yes		none	
54245	1	L	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	54	unknown, 83	10–100	yes (54)	no	unknown	unknown	unknown	breast cancer (76, 78), basalioma (63), carcinoid tumor (77)
54245	2	L	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	64	disease other than cancer		yes (64)	no	unknown	unknown	unknown	lung cancer (69)
54856	1	L	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	54	alive	10–100	no	yes (55)	no	no	none	breast cancer both sides (50)
54856	2	L	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	60	CRC (71)	unknown	yes (61)	no	unknown	unknown	unknown	
54856	3	L	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	66	CRC (68)	numerous	yes (66)	no	unknown	unknown	unknown	
54962	1	L	F	c.1187G>A; p.Gly396Asp	c.1214C>T; p.Pro405Leu	41	alive	50–100	no	yes (47)	no	no	none	
54962	2	L	F	c.1187G>A; p.Gly396Asp	c.1214C>T; p.Pro405Leu	51	alive	1	yes (51)	yes (55)	no	no	none	
55123	1	L	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	58	alive	30	yes (58)	yes (65)	no	no	fundic gland polyps	benign breast tumor (55)
55247	1	L	F	c.536A>G; p.Tyr179Cys	c.739 C>T; p.Arg247X	46	alive	50–100	yes (46)	yes (63)	no	no	none	
55356	1	L	F	c.1214C>T; p.Pro405Leu	c.1147delC; p.Ala385ProfsX25	40	unknown (70)	polyposis	yes (42)	yes (58)	no	no	none	

Supplementary Table 1. (Continued)

Patient no.	Index case (1)/relative	Center	Gender	Mutation 1	Mutation 2	Age[a] at diagnosis	Cause and age[a] at death	Maximal polyp number colorectum	Colorectal cancer (age[a])	Gastroduodenoscopy (age[a])	No. and histology of duodenal polyposis	Duodenal cancer	No. and type of gastric polyps	Extracolonic tumor (age[a] at diagnosis)
55535	1	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	45	CRC (45)	35	yes (45)	no	unknown	unknown	unknown	
56081	1	L	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	59	alive	>20	yes (59)	no	unknown	unknown	unknown	
56081	2	L	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	50	alive	20–25	yes (49)	no	unknown	unknown	unknown	
56081	3	L	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	58	alive	multiple	no	no	unknown	unknown	unknown	
56081	4	L	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	42	alive	multiple	no	yes (48)	no	no	none	
56351	1	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	34	alive	>100	no	yes (36)	yes		none	benign skin tumor
56566	1	L	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	67	alive	>100	yes (67)	yes (67)	no	no	none	
56566	2	L	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp		unknown if deceased		unknown	no	unknown	unknown	unknown	
56641	1	L	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	43	alive	10–50	yes (43)	yes (53)	no	no	none	benign endometrial tumor (57)
57135	1	L	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	45	CRC (49)	>25	yes (46)	no	unknown	unknown	unknown	basalioma (44)
57137	1	L	F	c.536A>G; p.Tyr179Cys	c.1147delC; p.Ala385ProfsX25	21	alive	36	yes (21)	yes (28)	no	no	none	
57139	1	L	M	c.1187G>A; p.Gly396Asp	c.1147delC; p.Ala385ProfsX25	42	alive	10–50	yes (42)	yes (61)	no	no	none	
57246	1	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	65	alive	10–100	yes (65)	yes (65)	2 adenomas	yes	none	
57249	1	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	49	alive	polyposis	yes (49)	yes (59)	no	no	none	esophagic cancer (59)
57249	2	L	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	48	alive	multiple	yes (49)	yes (49)	no	no	none	
57249	3	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	52	alive	numerous	yes (52)	yes (58)	no	no	none	
57308	1	L	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	44	disease other than cancer (47)	>15	no	no	unknown	unknown	unknown	
57449	1	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	45	alive	>100	yes (45)	yes (58)	no	no	none	sebaceous gland adenoma (68), benign skin tumor (74)
57591	1	L	M	c.1214C>T; p.Pro405Leu	c.933+3A>C	40	CRC (41)	50–100	yes (40)	no	unknown	unknown	unknown	
57976	1	L	F	c.536A>G; p.Tyr179Cys	c.1214C>T; p.Pro405Leu	49	unknown if deceased	12	no	no	unknown	unknown	unknown	
58746	1	L	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	27	alive	30–40	no	yes (29)	no	no	none	
60322	2	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	64	alive		yes	no	unknown	unknown	unknown	
60322	3	L	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	55	alive		yes	no	unknown	unknown	unknown	
60406	1	L	M	c.1437_1499delGGA; p.Glu480del	c.1437_1499delGGA; p.Glu480del	49	alive	10–100	yes (51)	no	unknown	unknown	unknown	
60406	2	L	M	c.1437_1499delGGA; p.Glu480del	c.1437_1499delGGA; p.Glu480del		unknown if deceased	30	no	yes (50)	no	no	fundic gland polyps	benign skin tumor (53)
62512	1	L	M	c.536A>G; p.Tyr179Cys	c.1214C>T; p.Pro405Leu	29	alive	30–40	no	no	unknown	unknown	unknown	benign skin tumor (38)
62805	1	L	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	63	alive	10–100	no	yes (67)	5 adenomas	no	fundic gland polyps	
65739	1	L	M	c.536A>G; p.Tyr179Cys	c.925C>T; p.Arg309Cys	63	alive	10–20	no	yes (58)	no	no	none	
67143	1	L	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	61	alive	20–50	yes (61)	yes (70)	no	no	none	benign skin tumor (54)
67143	2	L	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp		unknown if deceased		unknown	no	unknown	unknown	unknown	
1	1	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	31	alive	2	yes (36)	no	unknown	unknown	unknown	benign skin tumor (33)
1	2	C	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	40	alive	1	no	no	unknown	unknown	unknown	
2	1	C	F	c.1187G>A; p.Gly396Asp	c.933+3A>C	34	alive	>6	no	yes (35)	unknown		unknown	benign breast tumor (22)
2	2	C	F	c.1187G>A; p.Gly396Asp	c.933+3A>C	41	alive	20	no	unknown				
2	3	C	F	c.1187G>A; p.Gly396Asp	c.933+3A>C	57	alive	unknown	yes (57)	unknown				
2	4	C	F	c.1187G>A; p.Gly396Asp	c.933+3A>C		alive	multiple	no	no	unknown	unknown	unknown	ovarian cancer
2	5	C	M	c.1187G>A; p.Gly396Asp	c.933+3A>C		alive	a number of polyps	no	unknown				other benign tumors

Supplementary Table 1. (Continued)

Patient no.	Index case (1)/relative	Center	Gender	Mutation 1	Mutation 2	Age[a] at diagnosis	Cause and age[a] at death	Maximal polyp number colorectum	Colorectal cancer (age[a])	Gastroduodenoscopy (age[a])	No. and histology of duodenal polyposis	Duodenal cancer	No. and type of gastric polyps	Extracolonic tumor (age[a] at diagnosis)
3	1	C	F	c.1438G>T; p.Glu480X	c.1438G>T; p.Glu480X	51	alive	40–50	no	yes (48)	no	no	none	
4	1	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	47	alive	25–30	yes (47)	yes (50)	no	no	none	
5	1	C	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	36	alive	>100	yes (51)	unknown				
6	1	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	47	alive	20–50	no	no	unknown	unknown	unknown	
7	1	C	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	41	alive	156	no	no	unknown	unknown	unknown	
8	1	C	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	62	alive	70	yes (62)	unknown				
9	1	C	F	c.536A>G; p.Tyr179Cys	c.389-1G>A	56	alive	14	no	unknown				
10	1	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	48	unknown cause/age	<100	no	unknown				
11	1	C	M	c.312C>A; p.Tyr104X	c.312C>A; p.Tyr104X	51	alive	432	yes (51)	yes (55)	no	no	none	
12	1	C	M	c.1438G>T; p.Glu480X	c.1438G>T; p.Glu480X	37	CRC (38)	>25	yes (37)	yes (37)	yes; number/histology unknown	no	none	
12	2	C	F	c.1438G>T; p.Glu480X	c.1438G>T; p.Glu480X	44	alive	143	no	unknown				
12	3	C	F	c.1438G>T; p.Glu480X	c.1438G>T; p.Glu480X	36	alive	120	yes (36)	unknown				
13	1	C	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	45	alive	>10	no	no	unknown	unknown	unknown	
14	1	C	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	43	alive	3	yes (43)	yes (46)	no	no	none	
14	2	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	53	alive	>100	yes (61)	no	unknown	unknown	unknown	
14	3	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp		CRC (47)	multiple	yes (45)	no	unknown	unknown	unknown	
14	4	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp		CRC (43)	unknown	yes	unknown				
15	1	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	49	alive	50–100	no	no	unknown	unknown	unknown	
15	2	C	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	51	alive	multiple	no	no	unknown	unknown	unknown	
15	3	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	46	CRC (47)	2 adenomas in resection	yes (46)	unknown				
16	1	C	M	c.1187G>A; p.Gly396Asp	Gln338X	49	alive	multiple	no	no	unknown	unknown	unknown	
16	2	C	F	c.1187G>A; p.Gly396Asp	Gln338X	50	CRC (50)	19	yes (50)	unknown				
17	1	C	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	38	alive	multiple	yes (38)	no	unknown	unknown	unknown	
18	1	C	F	c.536A>G; p.Tyr179Cys	c.1518+2T>C	41	alive	multiple	yes (41)	no	unknown	unknown	unknown	breast cancer (71)
19	1	C	M	c.1438G>T; p.Glu480X	c.1438G>T; p.Glu480X	49	alive	200	no	yes (49)	no	no	none	benign skin tumor (55)
19	2	C	M	c.1438G>T; p.Glu480X	c.1438G>T; p.Glu480X		unknown (47)	unknown	unknown	unknown				
20	1	C	M	c.312C>A; p.Tyr104X	c.312C>A; p.Tyr104X	62	alive	>100	yes	yes (63)	no	no	none	
20	2	C	M	c.312C>A; p.Tyr104X	c.312C>A; p.Tyr104X	57	alive	>12	yes (59)	no	unknown	unknown	unknown	
20	3	C	F	c.312C>A; p.Tyr104X	c.312C>A; p.Tyr104X	38	alive	>100	no	no	unknown	unknown	unknown	
20	4	C	F	c.312C>A; p.Tyr104X	c.312C>A; p.Tyr104X	40	alive		unknown	no	unknown	unknown	unknown	
20	5	C	M	c.312C>A; p.Tyr104X	c.312C>A; p.Tyr104X	46	alive	>100	no	no	unknown	unknown	unknown	
21	1	C	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	35	alive	10–50	yes (45)	yes (49)	no	no	none	
21	2	C	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	53	CRC (53)	17	yes (53)	yes (53)	no	no	none	
22	1	C	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	65	CRC (69)	>100	yes (65)	unknown				
23	1	C	M	c.1438G>T; p.Glu480X	c.1438G>T; p.Glu480X	65	CRC (69)	>150	yes (65)	yes (65)	no	no	multiple polyps, histology unknown	kidney cysts
24	1	C	M	c.1187G>A; p.Gly396Asp	Asn238Ser	50	alive	multiple small sessile polyps	yes (50)	no	unknown	unknown	unknown	benign skin tumor (50)
25	1	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	65	alive	numerous	yes (65)	no	unknown	unknown	unknown	
26	1	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	46	alive	50–75	no	no	unknown	unknown	unknown	
26	2	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp		alive	few	no	unknown				
26	3	C	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	45	alive	>100	no	unknown				
26	4	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	41	alive	few	no	unknown				
26	5	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	44	disease other than cancer (46)	76	yes (44)	unknown				

Supplementary Table 1. (Continued)

Patient no.	Index case (1)/relative	Center	Gender	Mutation 1	Mutation 2	Age[a] at diagnosis	Cause and age[a] at death	Maximal polyp number colorectum	Colorectal cancer (age[a])	Gastroduodenoscopy (age[a])	No. and histology of duodenal polyposis	Duodenal cancer	No. and type of gastric polyps	Extracolonic tumor (age[a] at diagnosis)
27	1	C	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	45	alive	numerous	yes (45)	yes (59)	no	no	none	
28	1	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	52	alive	20–30	no	yes (62)	no	no	none	cancer of soft palate (46), carcinoid tumor (62)
29	1	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	44	alive	>20	no	yes (45)	no	no	none	sebaceous gland adenoma (28)
30	1	C	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	36	alive	4	yes (37)	yes (38)	no	no	none	
31	1	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	12	gastric cancer (17)	>100	no	yes (17)	no	no	none	gastric cancer (17)
31	2	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	14	alive	>100	no	yes (14)	unknown		none	
32	1	C	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	58	CRC (60)	multiple	yes (58)	yes (59)	no	no	none	
33	1	C	M	c.1438G>T; p.Glu480X	c.1438G>T; p.Glu480X	55	disease other than cancer (69)	multiple	yes (55)	yes (55)	no	no	none	
34	1	C	M	c.1187G>A; p.Gly396Asp	c.647G>A; p.Gly216Glu	65	alive	22	yes (67)	no	unknown	unknown	unknown	
35	1	C	M	c.1187G>A; p.Gly396Asp	c.1101del, p.Arg368GlyfsX40	36	alive	multiple	yes (36)	yes (43)	no	no	3 adenomas	
36	1	C	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	43	alive	19	yes (43)	yes (44)	no	no	none	
36	2	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp		alive	unknown	unknown	unknown				
36	3	C	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp		alive	unknown	unknown	unknown				
36	4	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp		CRC	unknown	yes	unknown				
37	1	C	F	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	57	alive	10	yes (57)	yes (64)	no	no	none	lipoma
37	2	C	M	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	62	CRC (62)	unknown	yes (62)	yes (62)	no	no	none	
38	1	C	F	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	50	alive	123	no	no	unknown	unknown	unknown	
38	2	C	F	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp		CRC	unknown	unknown	unknown				
38	3	C	F	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp		alive	unknown	yes	unknown				
39	1	C	M	c.536A>G; p.Tyr179Cys	c.1147delC; p.Ala385ProfsX25	53	CRC (57)	11–30	yes (53)	no	unknown	unknown	unknown	
40	1	C	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	50	unknown (52)	50	yes (50)	unknown				
41	1	C	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	33	alive	50–100	no	no	unknown	unknown	unknown	
42	1	C	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	30	alive	multiple	yes (30)	yes (30)	>10 adenomas	no	few; one adenoma	
42	2	C	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	29	alive	multiple	no	unknown				
42	3	C	M	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	28	alive	>100	no	unknown				
43	1	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	49	alive	multiple	no	no	unknown	unknown	unknown	
43	2	C	M	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp		alive	unknown	unknown	unknown				
44	1	C	M	c.536A>G; p.Tyr179Cys	Trp131Arg	30	alive	152	no	no	unknown	unknown	unknown	
45	1	C	M	c.536A>G; p.Tyr179Cys	c.933+3A>C	46	alive	119	yes (47)	no	unknown	unknown	unknown	skin cancer (45)
46	1	C	F	c.536A>G; p.Tyr179Cys	c.690 G>A; p.Gln230Gln	47	alive	200	yes (48)	yes (50)	no	no	none	
47	1	C	F	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	53	alive	15	yes (53)	no	unknown	unknown	unknown	
48	1	C	M	c.536A>G; p.Tyr179Cys	c.690 G>A; p.Gln230Gln	42	alive	120	no	yes (43)	no	no	none	sebaceous gland adenoma (45), other benign tumors (47)

Supplementary Table 1. (Continued)

Patient no.	Index case (1)/relative	Center	Gender	Mutation 1	Mutation 2	Age[a] at diagnosis	Cause and age[a] at death	Maximal polyp number colorectum	Colorectal cancer (age[a])	Gastroduodenoscopy (age[a])	No. and histology of duodenal polyposis	Duodenal cancer	No. and type of gastric polyps	Extracolonic tumor (age[a] at diagnosis)
50	1	C	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	31	alive	88	yes (57)	no	unknown	unknown	unknown	
51	1	C	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	33	alive	13	yes (60)	no	unknown	unknown	unknown	
52	1	C	F	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	48	alive	multiple	yes (48)	yes (63)	no	no	none	carcinoid tumor (49)
53	1	C	M	c.1147delC; p.Ala385ProfsX25	c.1147delC; p.Ala385ProfsX25	45	alive	>100	yes (45)	no	unknown	unknown	unknown	
53	2	C	M	c.1147delC; p.Ala385ProfsX25	c.1147delC; p.Ala385ProfsX25	51	alive	30–40	yes (51)	no	unknown	unknown	unknown	
54	1	C	F	c.1187G>A; p.Gly396Asp	Arg245His	48	alive	22	yes (41)	no	unknown	unknown	unknown	carcinoid tumor (42)

B, Institute of Human Genetics, Bonn, Germany; C, Institute of Medical Genetics, Cardiff, UK; CRC, colorectal cancer; L, Centre for Human and Clinical Genetics, Leiden, The Netherlands; F, female; M, male.
[a]Age is in years.

Supplementary Table 2. Histology and Age at Diagnosis in the 38 *MUTYH*-Associated Polyposis Patients Affected by Extracolonic Cancer

Patient no.	Cancer	Gender	Age (y) at diagnosis	Histology result	Origin
57249	Esophagus	M	59	Barrett carcinoma	Dutch
676	Esophagus	M	46	Carcinoma in situ	German
1293	Stomach	F	48	Early cancer mucosal type	German
548	Stomach	M	38	Adenocarcinoma	German
31	Stomach	M	17	Gastric cancer	UK
57246	Duodenum	M	65	Adenocarcinoma	Dutch
19221	Duodenum	M	56	Adenocarcinoma	Dutch
19049-3	Bladder	M	67	Papillar urothelial carcinoma (grade I–II)	Dutch
858	Bladder	M	62	Urothelial carcinoma	German
19049-1	Bladder	M	60	Papillar urothelial carcinoma (grade II)	Dutch
526	Bladder	F	45	Squamous cell carcinoma	German
10	Skin	M	59	Melanoma	German
885	Skin	F	32	Melanoma	German
19221	Skin	M	30	Melanoma	Dutch
561	Skin	F	68	Spinalioma (spinous cell carcinoma)	German
395	Skin	M	60	Spinalioma (spinous cell carcinoma)	German
52105	Skin	M	71	Basalioma (basal cell carcinomas)	Dutch
54245	Skin	F	63	Basalioma (basal cell carcinoma)	Dutch
858	Skin	M	62	Basalioma (basal cell carcinoma)	German
53276	Skin	M	58	Basalioma (basal cell carcinoma)	Dutch
1111	Skin	M	48	Basalioma (basal cell carcinoma)	German
45	Skin	M	45	Basalioma (basal cell carcinoma)	UK
57135	Skin	F	44	Basalioma (basal cell carcinoma)	Dutch
54186	Skin	F	41	Basalioma (basal cell carcinoma)	Dutch
787	Breast	M	56	Breast cancer	German
54245	Breast	F	76	Intracystic papillary carcinoma	Dutch
			78	Ductal carcinoma (unilateral)	
18	Breast	F	71	Infiltrating ductal carcinoma (grade II)	UK
561	Breast	F	60	Intracystic papillary carcinoma	German
			68	Ductal carcinoma (unilateral)	
52240	Breast	F	55	Ductal carcinoma in situ	Dutch
54140	Breast	F	50	Breast cancer	Dutch
1358	Breast	F	49	Lobular differentiated with intratumoral DCIS	German
54856	Breast	F	50	Right: lobular carcinoma with an in situ component and a DCIS component; left: DCIS	Dutch
1293	Breast	F	45	Invasive ductal cancer	German
489	Ovary	F	56	Ovarian carcinoma	German
1412	Ovary	F	45	Mucinous cystadenocarcinoma	German
2	Ovary	F	?	Ovarian carcinoma	UK
1323	Endometrium	F	54	Adenocarcinoma	German
1412	Endometrium	F	47	Endometrium carcinoma	German

DCIS, ductal carcinoma in situ; F, female; M, male.