

Clinical and molecular aspects of MUTYH- and APCassociated polyposis

Nielsen. M.

Citation

Nielsen, M. (2011, March 10). *Clinical and molecular aspects of MUTYH-and APC-associated polyposis*. Retrieved from https://hdl.handle.net/1887/16611

Version: Corrected Publisher's Version

Licence agreement concerning inclusion of doctoral

License: thesis in the Institutional Repository of the

University of Leiden

Downloaded from: https://hdl.handle.net/1887/16611

Note: To cite this publication please use the final published version (if applicable).

2.3

Expanded extracolonic tumor spectrum in *MUTYH*-associated polyposis

Vogt S

Jones N

Christian D

Engel C

Nielsen M

Kaufmann A

Steinke V

asen HF

Propping P

Sampson JR

Hes FJ

Aretz S

Gastroenterology. 2009 Dec;137(6):1976-85

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.

90

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 (MUTYH) 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 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-todate 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 previously¹⁵ 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).

92 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 (personyears) 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

Table 1. Baseline Data of the 3 Patient Groups

				Comb	ined no. of patie	ents
	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)

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 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).

Table 2. Gastroduodenal Findings

					Median age at	
	Germany	UK	Netherlands	All patients	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	Fc	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	3e	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)

Cl, 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.

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 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).

^aInclude also extraintestinal malignancies, which were observed only once.

blnclude melanoma, spinous cell carcinoma, and basal cell carcinoma.

Data related to female MUTYH-associated polyposis patients only.

^dRelated to affected females (n = 8) and total number of breast cancers (n = 11).

^oAge 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.

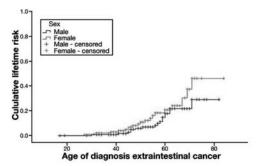


Figure 1. Cumulative lifetime risks for extraintestinal cancer in MUTYH-associated polyposis (MAP) patients.

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 4A.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 significantly 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.

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	_	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 tumorsc	4 (2/48)	3 (1/34 F)	2.7 (1/36)	3.5 (4/118 F)	43 (22-59)

In 3 of 8 cases, a second metachronous or synchronous breast cancer occurred (F, female).

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 4B). Interestingly,

bAll 11 breast cancers.

^cAll data related to female MUTYH-associated polyposis patients only.

Fibrous histiocytoma, capillary hemangioma, pilar cyst, dermatofibroma, follicle cyst,

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 4B). 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 patients (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 cancer²⁶ suggests that defects in the base excision repair pathway may be relevant in development of some gastric cancers.

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

^aSome patients are listed more than once depending on the distribution of duodenal polyps.

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. 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

bOutside periampullary region.

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. 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), 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 tumors⁴³; 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 patients⁴⁶; 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 extra-colonic 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. 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.

References

- Al-Tassan N, Chmiel NH, Maynard J, et al. Inherited variants of MUTYH associated with somatic G:C_iT:A mutations in colorectal tumors. Nat Genet 2002;30:227–232.
- Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MUTYH. N Engl J Med 2003;348:791–799.
- Sampson JR, Dolwani S, Jones S, et al. Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of MUTYH. Lancet 2003;362:39–41.
- Fleischmann C, Peto J, Cheadle J, et al. Comprehensive analysis of the contribution of germline MUTYH variation to early-onset colorectal cancer. Int J Cancer 2004;109:554–558.
- Aretz S, Uhlhaas S, Goergens H, et al. MUTYH-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. Int J Cancer 2006;119:807–814.
- Gismondi V, Meta M, Bonelli L, et al. Prevalence of the Y165C, G382D and 1395delGGA germline mutations of the MUTYH gene in Italian patients with adenomatous polyposis coli and colorectal adenomas. Int J Cancer 2004;109:680–684.
- Isidro G, Laranjeira F, Pires A, et al. Germline MUTYH (MUTYH) mutations in Portuguese individuals with multiple colorectal adenomas. Hum Mutat 2004;24:353–354.
- Wang L, Baudhuin LM, Boardman LA, et al. MUTYH mutations in patients with attenuated and classic polyposis and with young-onset colorectal cancer without polyps. Gastroenterology 2004; 127:9–16.
- Eliason K, Hendrickson BC, Judkins T, et al. The potential for increased clinical sensitivity in genetic testing for polyposis colorectal cancer through the analysis of MUTYH mutations in North American patients. J Med Genet 2005;42:95–96.
- Venesio T, Molatore S, Cattaneo F, et al. High frequency of MUTYH gene mutations in a subset of patients with familial adenomatous polyposis. Gastroenterology 2004;126:1681–1685.
- Kairupan CF, Meldrum CJ, Crooks R, et al. Mutation analysis of the MUTYH gene in an Australian series
 of colorectal polyposis patients with or without germline APC mutations. Int J Cancer 2005;116:73–77.
- 12. Nielsen M, Franken PF, Reinards TH, et al. Multiplicity in polyp count and extracolonic manifestations in 40 Dutch patients with *MUTYH* associated polyposis coli (MAP). J Med Genet 2005;42: e54.
- 13. Galiatsatos P, Foulkes WD. Familial adenomatous polyposis. Am J Gastroenterol 2006;101:385–398.
- 14. Farrington SM, Tenesa A, Barnetson R, et al. Germline susceptibility to colorectal cancer due to base-excision repair gene defects. Am J Hum Genet 2005;77:112–119.
- Nielsen M, Joerink-van de Beld MC, Jones N, et al. Analysis of MUTYH genotypes and colorectal phenotypes in patients with MUTYH-associated polyposis. Gastroenterology 2009;136:471–476.
- Ponti G, Ponz de Leon M, Maffei S, et al. Attenuated familial adenomatous polyposis and Muir-Torre syndrome linked to compound biallelic constitutional MUTYH gene mutations. Clin Genet 2005:68:442-447.
- Baglioni S, Melean G, Gensini F, et al. A kindred with MUTYH-associated polyposis and pilomatricomas.
 Am J Med Genet A 2005;134:212–214.
- Buecher B, Baert-Desurmont S, Leborgne J, et al. Duodenal adenocarcinoma and Mut Y human homologue-associated polyposis. Eur J Gastroenterol Hepatol 2008;20:1024–1027.
- Jones S, Emmerson P, Maynard J, et al. Biallelic germline mutations in MUTYH predispose to multiple colorectal adenoma and somatic G:C_iT:A mutations. Hum Mol Genet 2002;11:2961–2967.
- Nielsen M, Poley JW, Verhoef S, et al. Duodenal carcinoma in MUTYH-associated polyposis. J Clin Pathol 2006;59:1212–1215.
- Kanter-Smoler G, Bjork J, Fritzell K, et al. Novel findings in Swedish patients with MUTYH-associated polyposis: mutation detection and clinical characterization. Clin Gastroenterol Hepatol 2006;4: 499– 506.

- Offerhaus GJ, Entius MM, Giardiello FM. Upper gastrointestinal polyps in familial adenomatous polyposis. Hepatogastroenterology1999;46:667–669.
- 23. Burt RW. Gastric fundic gland polyps. Gastroenterology 2003;125:1462-1469.
- Kadmon M, Tandara A, Herfarth C. Duodenal adenomatosis infamilial adenomatous polyposis coli.
 A review of the literatureand results from the Heidelberg Polyposis Register. Int J Colorectal Dis 2001:16:63-75.
- 25. Bülow S, Bjork J, Christensen IJ, et al. Duodenal adenomatosis in familial adenomatous polyposis. Gut 2004:53:381–386.
- Kim CJ, Cho YG, Park CH, et al. Genetic alterations of the MUTYH gene in gastric cancer. Oncogene 2004;23:6820–6822.
- 27. Wallace MH, Phillips RK. Upper gastrointestinal disease in patients with familial adenomatous polyposis. Br J Surg 1998;85: 742–750.
- Offerhaus GJ, Giardiello FM, Krush AJ, et al. The risk of upper gastrointestinal cancer in familial adenomatous polyposis. Gastroenterology 1992;102:1980–1982.
- asen HF, Bulow S, Myrhoj T, et al. Decision analysis in the management of duodenal adenomatosis in familial adenomatous polyposis. Gut 1997;40:716–719.
- Aarnio M, Sankila R, Pukkala E, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes.
 Int J Cancer 1999;81: 214–218.
- Sijmons RH, Kiemeney LA, Witjes JA, et al. Urinary tract cancer and hereditary nonpolyposis colorectal cancer: risks and screening options. J Urol 1998;160:466–470.
- 32 Vasen HF, Stormorken A, Menko FH, et al. MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: a study of hereditary nonpolyposis colorectal cancer families. J Clin Oncol 2001:19:4074–4080.
- 33. Myrhoj T, Andersen MB, Bernstein I. Screening for urinary tract cancer with urine cytology in Lynch syndrome and familial colorectal cancer. Fam Cancer 2008;7:303–307.
- 34. Sieber OM, Howarth KM, Thirlwell C, et al. *MUTYH* deficiency enhances intestinal tumorigenesis in multiple intestinal neoplasia (*APC*Min/) mice. Cancer Res 2004;64:8876–8881.
- Le Page F, Randrianarison V, Marot D, et al. BRCA1 and BRCA2 are necessary for the transcriptioncoupled repair of the oxidative 8-oxoguanine lesion in human cells. Cancer Res 2000;60:5548-5552.
- Beiner ME, Zhang WW, Zhang S, et al. Mutations of the MUTYH gene do not substantially contribute to the risk of breast cancer. Breast Cancer Res Treat 2009;114:575–578.
- Barnetson RA, Devlin L, Miller J, et al. Germline mutation prevalence in the base excision repair gene, MUTYH, in patients with endometrial cancer. Clin Genet 2007;72:551–555.
- 38. Tricarico R, Bet P, Ciambotti B, et al. Endometrial cancer and somatic G T KRAS transversion in patients with constitutional *MUTYH* biallelic mutations. Cancer Lett 2009;274:266–270.
- 39. Campbell WJ, Spence RA, Parks TG. The role of congenital hypertrophy of the retinal pigment epithelium in screening for familial adenomatous polyposis. Int J Colorectal Dis 1994;9:191–196.
- 40. Giardiello FM, Petersen GM, Piantadosi S, et al. *APC* gene mutations and extraintestinal phenotype of familial adenomatous polyposis. Gut 1997;40:521–525.
- Mangold E, Pagenstecher C, Leister M, et al. A genotype-phenotype correlation in HNPCC: strong predominance of msh2 mutations in 41 patients with Muir–Torre syndrome. J Med Genet 2004;41:567– 572
- South CD, Hampel H, Comeras I, et al. The frequency of Muir–Torre syndrome among Lynch syndrome families. J Natl Cancer Inst 2008;100:277–281.
- 43. Entius MM, Keller JJ, Drillenburg P, et al. Microsatellite instability and expression of hMLH-1 and hMSH-2 in sebaceous gland carcinomas as markers for Muir–Torre syndrome. Clin Cancer Res 2000;6:1784–1789.

- ruse R, Rutten A, Lamberti C, et al. Muir–Torre phenotype has a frequency of DNA mismatch-repairgene mutations similar to that in hereditary nonpolyposis colorectal cancer families defined by the Amsterdam criteria. Am J Hum Genet 1998;63:63–70.
- 45. Ajith Kumar VK, Gold JA, Mallon E, et al. Sebaceous adenomas in an *MUTYH* associated polyposis patient of Indian (Gujarati) origin. Fam Cancer 2008;7:187–189.
- 46. Heinimann K, Mullhaupt B, Weber W, et al. Phenotypic differences in familial adenomatous polyposis based on *APC* gene mutation status. Gut 1998;43:675–679.
- 47. Pujol RM, Casanova JM, Egido R, et al. Multiple familial pilomatricomas: a cutaneous marker for Gardner syndrome? Pediatr Dermatol 1995;12:331–335.
- 48. Urabe K, Xia J, Masuda T, et al. Pilomatricoma-like changes in the epidermoid cysts of Gardner syndrome with an APC gene mutation. J Dermatol 2004;31:255–257.
- 49. Chuang CC, Lin HC. Pilomatrixoma of the head and neck. J Chin Med Assoc 2004;67:633-636.
- Kairupan C, Scott RJ. Base excision repair and the role of MUTYH. Hered Cancer Clin Pract 2007;5:199-209.
- Mazurek A, Berardini M, Fishel R. Activation of human MutS homologs by 8-oxo-guanine DNA damage.
 J Biol Chem 2002;277: 8260–8266.
- Gu Y, Parker A, Wilson TM, et al. Human MutY homolog, a DNA glycosylase involved in base excision repair, physically and functionally interacts with mismatch repair proteins human MutS homolog 2/ human MutS homolog 6. J Biol Chem 2002;277:11135–11142.
- 53. Russo MT, De Luca G, Degan P, et al. Different DNA repair strategies to combat the threat from 8-oxoguanine. Mutat Res 2007;614:69-76.
- 54. Giardiello FM, Offerhaus GJ, Lee DH, et al. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. Gut 1993;34:1394–1396.
- Goecke T, Schulmann K, Engel C, et al. Genotype-phenotype comparison of German MLH1 and MSH2 mutation carriers clinically affected with Lynch syndrome: a report by the German HNPCC Consortium. J Clin Oncol 2006:24:4285–4292.
- Vasen HF, Moslein G, Alonso A, et al. Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut 2008;57:704–713.
- Albert USH. Stufe-3-Leitlinie Brustkrebs-Früherkennung in Deutschland. 1. Aktualisierung 2008. W. Zuckschwerdt Verlag München, Wien, New York. Available at: http://leitlinien.net.Accessed February 2008.
- 58. Perry N, Broeders M, de Wolf C, et al. European Guidelines for quality assurance in breast cancer screening and diagnosis. 4th ed. Luxembourg: Office for Official Publications of the European Communities, 2006.
- Otto SJ, Fracheboud J, Looman CW, et al. Initiation of populationbased mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 2003;361:1411– 1417.
- 60. Dove-Edwin I, Boks D, Goff S, et al. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. Cancer 2002;94:1708–1712.
- Bastacky S, Ibrahim S, Wilczynski SP, et al. The accuracy of urinary cytology in daily practice. Cancer 1999;87:118–128.

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

. CE	(T)/relative Center Gender	1000	Gender	Mutation 1	Mutation 2	diagnosis	diagnosis age at death	number colorectum	cancer (age ³)	(age ^a)	duodenal polyposis	cancer	(age ^a) duodenal polyposis cancer gastric polyps	(age ^a at diagnosis)
						,		- 1						
10	н	ш	Σ	c.749G>A; p.Gly250Asp c.1147delC; p.Ala385i	c.1147delC; p.Ala385ProfsX25	37	alive	multiple	Yes (50)	yes	no	00	none	
10	2	ш	Σ	c.749G>A; p.Gly250Asp c.1147delC;	c.1147delC;	43	alive	unknown	01	yes	unknown	ou 0	unknown	melanoma (59)
56	+	ш	ш	p.Ala385Pf015A25 c.536A>G; p.Tyr179Cys c.1437_1499delGGA; p.Glu480del	p.Ala385ProtsA25 c.1437_1499delGGA; p.Glu480del	59	alive	multiple	yes (29)	yes (37)	NO	0	none	
56	7	ш	ш	c.536A>G; p.Tyr179Cys c.1437_1499delGGA; p.Glu480del	c.1437_1499delGGA; p.Glu480del	83	alive	250	yes (33)	yes (36)	1 adenoma	0	none	lipoma (30), 2 other benign tumors (33), dermoid cyst (33), hepatic cysts
56	е	В	ш	c.536A>G; p.Tyr179Cys c.1437_1499delGGA; p.Glu480del	c.1437_1499deIGGA; p.Glu480deI	33	alive	20	OU	yes (45)	No	О	none	lipoma
94 370	H H	<u>в</u> в	ш ш	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp c.536A>G; p.Tyr179Cys c.1147delC; p.Ala385ProfsX25	c.1187G>A; p.Gly396Asp c.1147delC; p.Ala385ProfsX25	29	alive	>100	9 9	no yes (41)	unknown 1 adenoma	unknown no	unknown none	benign skin tumor (15), maxillary cysts (21)
395	+	ш	Σ	c.1187G>A; p.Gly396Asp	c.1214C>T; p.Pro405Leu	34		unknown	ОП	yes (49)	NO	no	none	benign skin tumor (50), spinalioma (60)
398	₩	ш	ш	cys	c.734G>A; p.Arg245His	43	alive	500-1000	yes (44)	yes (44)	few polyps, histology unknown	01 .	none	
415	₩ ₹	ω α	Σ μ	c.504+19_31del13	c.734G>A; p.Arg245His	53	alive	>100	yes (49)	yes	00	00	none	none 4 moltan biothology (E4), quantitati
n	4	۵	_	coopy of bright lacks	c.ttord.h, p.dysoonsp	g S	DAIID DAI	000-001	≘	yes (43)	2	≘	ı poryp, ilistology unknown	cancer (56), benign skin tumor (56)
489	7	В	ш	c.536A>G; p.Tyr179Cys o	c.536A>G; p.Tyr1.79Cys c.1187G>A; p.Gly396Asp	45	alive	100	yes (46)	yes (45)	Ou	no	none	lipoma (37), hepatic cysts (48)
526	1	В	ш	c.536A>G; p.Tyr179Cys c.933+3A>C	c.933+3A>C	41	alive	50-100	yes (41)	yes (41)	yes	no	none	bladder carcinoma (45)
co.	2	ш	ш	c.536A>G; p.Tyr1.79Cys c.933+3A>C	c.933+3A>C	27	alive	<20	yes (38)	yes (25)	2 adenomas	no	none	jaw-bone cysts (10)
oc	₽	В	Σ	c.734G>A; p.Arg245His c.1147delC;	c.1147delC; n Ala385Profex25	36	gastric cancer	100-200	no Ou	yes (32)	NO	no	none	gastric cancer (38)
620	4	ш	Σ	c.1187G>A;	c.1187G>A; p.Gly396Asp	09	alive	>100	yes (60)	yes (60)	ou	no	none	
641	H	ш	ш	c.536A>G; p.Tyr179Cys c.1147delC; p.Ala385F	c.1147delC; p.Ala385ProfsX25	31	alive	20	OU	yes (31)	ou ou	no	none	maxillary cysts (23), benign breast tumor
,	,		:	Carolina Control	0.40.000	Č	-	000	į					(31)
099		<u>а</u> ш	ΣΣ	c.536A>G; p.1yr179Cys o	c.536A>G; p.1yr179Cys c.333+3A>C c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	46	alive	200	yes (52) yes (46)	yes (52) yes (46)	0 Q	2 2	none 1 polyp, histology unknown	
990	0	00	Σ	c.536A>G: p.Tvr179Cvs c.1187G>A: p.Glv396Asp	c.11876>A: p.Glv396Asp	45	alive	>50	00	ves (24)	JU	00	none	
099	1 4	ш	ш	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	41	alive	multiple	2 2	00	unknown	unknown	unknown	
099	2	ш	ш	c.536A>G; p.Tyr179Cys c	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	43	CRC (43)	multiple	yes (43)	по	unknown	unknown	unknown	
10	н	20	Σ	c.118/G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	90 PN	unknown (52)	30-40	0	yes (46)	UQ Q	00	none	esophagic cancer (46)
869	₩,	m	Σι	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	49		multiple	yes (49)	yes (53)	01.	ou 0	none	
n	Η.	m	ш	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	47	alive	150	yes (47)	yes (47)	1 adenoma	00	few fundic gland	few fundic gland hepatic cysts (47) nolyns
757 760		ш ш	шш	r179Cys	c.933+3A>C c.1187G>A; p.Gly396Asp	40	alive	50-100 5	no yes (57)	yes (40) yes (61)	OU OU	0 0	none	jaw-bone cysts (14)
774	4	ш	Σ		c.1187G>A; p.Gly396Asp	8	alive	>40	ОП	ОП	unknown	unknown	unknown	
982	H	ш	ш	p.Gly396Asp c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	39	alive	30	OU	yes (39)	по	OU	none	
787	7	В	Σ		c.1187G>A; p.Gly396Asp	51	alive	100-500	OU	yes (56)	4 polvps, histology	00	none	breast cancer (56)

no. (1)	Patient Index case no. (1)/relative	Center Gender	Gender	Mutation 1	Mutation 2	Age" at diagnosis	Age at Cause and diagnosis age at death	Maximal polyp number colorectum	Colorectal cancer (age²)	Gastroduodenoscopy No. and histology of Duodenal (age*) duodenal polyposis cancer	No. and histology of duodenal polyposis	Duodenal cancer	No. and type of gastric polyps	Extracolonic tumor (age" at diagnosis)
١.	,	,		0000	4 0000		1	007		1200				
818	н с	20 0		c.536A>G; p.1yr1 / 9Cys c.118 / G>A; p.Gly396Asp	c.118/G>A; p.Gly396Asp		alive	>100 	0 0	yes (37)	10 1 odonomo	0 6	none	
826	+ +	0 00	E LL	c.536A>G; p.Tyr179Cys c.933+3A>C	c.933+3A>C	78	alive	multiple	2 2	yes (35)	1 adenoma	2 2	3 adenomas	adenoma small
														bowel (49)
826	7	ω ,		p.Tyr179Cys	c.933+3A>C	31	alive	40	yes (31)	yes	no .	00	none	•
	Н	m	_	c.1147delC; c	c.1437_1499delGGA; p.Glu480del	89	alive	100-500	yes (38)	yes (60)	>15 adenomas	0	none	lipoma (65)
858	1	В	Σ	sk	3	49	alive	>150	yes (49)	yes (49)	no	01	none	bladder carcinoma (62),
					p.Gly276_Gly277insAla,Gly									basalioma (62)
	₽,	ω (c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys		alive	50-100	ou ou	yes (37)	3 adenomas	00	none	
	Η :	20		en en	c.118/G>A; p.Gly396Asp		alive	<100	yes (46)	yes (46)	ou 0	9	none	melanoma (32)
	ᆏ .	ω ,			c.1214C>T; p.Pro405Leu		alive	unknown	yes (51)	yes (51)	ou .	ou 0	none	testicular cancer (41)
925	Η.	20		c.536A>G; p.lyr1/9Cys c	c.536A>G; p.1yr1 /9Cys		CRC (51)	36	yes (48)	yes (48)	many adenomas	00	none	benign skin tumor (15)
	н (20 (c.536A>G; p.lyr1/9Cys o	c.118/G>A; p.Gly396Asp		alive	21-50	ou Ou	yes (54)	ou .	<u>و</u> .	none .	
		ם מ		c.536A>G; p.1yr1/9Cys c.118/G>A; p.Gly396Asp	C.I.I.87G>A; p.Gly396Asp	5 6	alive	71-50	yes (43)	0	unknown	unknown	unknown	
	⊣ ₹	20 00	Σμ	0.030A>4; p.lyr1/90ys 0.030A>4; p.lyr1/90ys	c.536A>4; p.1yr1/9cys	8 6	alive	multiple	yes (54)	yes (54)	no metanomia	OU Outland	none	
1	4	۵		coord i, priozocea	p.Glu480del	9	DAILE	200	(ee) (ee)	2		I I	THE CONTRACTOR OF THE CONTRACT	
	+	В		c.536A>G; p.Tyr179Cys c	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	48	alive	500-1000	yes (48)	yes (49)	no	ou 0	none	
1065	1	В	ш	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	42	alive	unknown	yes (42)	yes (50)	no	ou	none	benign skin tumor (36),
														benign endometrial tumor (48)
1065	2	В	Σ	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	28	alive	50-100	no	yes (28)	no	no	none	
	7	В		c.820C>T; p.Arg274Trp c	c.1518+2T>C	09		unknown	no	yes (55)	no	ou Ou	none	
1077	Ŧ	ш		c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	44	alive	50-100	no	0	unknown	unknown	unknown	
	7	ω :	Σ	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp		alive	09	yes (64)	02	unknown	unknown	unknown	hepatic cysts (70)
1083	⊣ .	ш і		c.536A>G; p.Tyr179Cys c.1012C>T; p.Gln338X	c.1012C>T; p.Gln338X	24	alive	50-100	00	yes (25)	no	9	none	
	Α,	m 1	Σ:	c.536A>G; p.1yr1/9Cys c.536A>G; p.1yr1/9Cys	c.536A>G; p.Tyr1.79Cys	54	CRC (55)	>100	yes (54)	yes (54)	ou	0	none	b-cell lymphoma (46)
		n		c.536A>G; p.1yr1/9Cys c.11/1C>1; p.GIN391X	C.11/1C>I; p.GIN391X	94	alive	07-06	9	yes (44)	unknown number or adenomas	2	o rundic giand polvps	
1111	4	В	Σ	c.536A>G; p.Tyr179Cys c.1171C>T; p.Gln391X	c.1171C>T; p.Gln391X	42	alive	100	yes (43)	yes (52)	ou	ou	none	basalioma (48, 51, 53)
1114	4	В		c.734G>A; p.Arg245His c.1147delC;	c.1147delC;	63	alive	500-1000	yes (68)	. 0	unknown	unknown	unknown	gangliocystoma (52)
1114	0	œ	ш	p.Alababa c 734G>A n Ara245His c 1147delC:	p.AlasosProisAzs	99	CRC (68)	IInknown	(99) 590	2	IInknown	IInknown	IInknown	
	4	2			p.Ala385ProfsX25	3	(00) 0110		(00)	2				
1114	8	8	Σ	c.734G>A; p.Arg245His c.1147delC;	c.1147delC;		CRC (63)	unknown	yes (63)	unknown				
1125	+	œ	ш	p.Ala385ProfsX25 c 5364>G: n Tvr179Cvs c 1187G>A: n Glv396Asn	p.Ala385ProfsX25 c.1187G>A: n.Glv396Asn	8	alive	6-10	vec (30)	ves (51)	2 adenomas	9	9000	henion breast
		1							(20) 226	(10) 006		2		tumor (59)
1126	1	В	ш	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	38	alive	>100	yes (38)	yes (38)	по	91	fundic gland	
1175	-	œ		c.5364>G: p.Tvr1790vs. c.734G>A: p.Arg245His	2.734G>A: p.Arg245His	36	alive	8	ol o	ves (36)	0	9	polyp	
1175	10		. ш	c.536A>G: n Tvr1 79Cvs c.734G>A: n Arg245His	734G>Ar n Arg245His	8 9	alive	<100	21.	yes (40)	2 0	2 2	1 adenoma 2	henion skin tumor (36)
	ı	1				2			2	(2)	<u>:</u>	}	fundic gland polvps	
1180	4	В	Σ	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	32	alive	<100	yes (47)	yes (47)	no	no	none	sebaceous gland
1211	Ħ	В	ш	c.1147delC;	c.1187G>A; p.Gly396Asp	37	alive	>20	yes (37)	yes (61)	01	ou	none	chinicilonia (OT)
1222	Ŧ	ш	Σ	c.734G>A; p.Arg245His c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	52	alive	70	yes (52)	yes (53)	no	ou	none	sebaceous gland
1229	+		Σ	6.1187G>A:	c.1187G>A: p.Glv396Asp	63	alive	>50	ves (63)	9	unknown	unknown unknown	unknown	benign tumors (48) kidney and hepatic (64)
,	1	1		p.Gly396Asp				3	(00)006	2				
12/1														

Supplementary Table 1. (Continued)

1		١														
1	Patient no.	Inde (1)/r	ex case relative Ce	inter Ger	nder	Mutation 1		Age* at liagnosis	Cause and age at death		Colorectal G cancer (age ^a)	iastroduodenosco (age³)	py No. and histology of duodenal polyposis	Duodenal	No. and type of gastric polyps	
1	1241					c.536A>G; p.Tyr179Cys c.1187G c.536A>G; p.Tyr179Cys c.536A>	3>A; p.Gly396Asp >G; p.Tyr179Cys	53	alive		no yes (48)	yes (53) yes (47)	0.00	01 01	none fundic gland	pancoast tumor (51)
1	1258					, 5364 / G. p. Tyrd 790 / 6 / 5364 /	5. p. Turd 790.ce	40	orlice		voc (40)	(40)	G	S	polyp	
1	1260					c.628C>T; p.Gln210X c.1147de	JelC;	4 4	alive		no no	yes (48)	2 polyps, histology	2 2	none	
1	1286		-			p.Alać 5.868G: p.Tvrt 790.e. p.12140	1385ProfsX25	9	aliva	S	8	S	unknown		umbudui	
1 1 1 1 1 1 1 1 1 1	1286					::536A>G: p.Tvr179Cvs c.1214C	3>T; p.Pro405Leu	8 4			2 2	ves (51)	0		none	
1	1293		1			c.536A>G; p.Tyr179Cys c.933+3	3A>C	45		nultiple	yes (45)	yes (45)	No		none	thyroid cancer (38),
1 1 1 1 1 1 1 1 1 1																breast cancer (45) gastric cancer (48)
2 B F c.463.1G-C c.11870-LCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCC	1309		₽				delC;	32	alive	75	no	yes (32)	по	ou	none	lipoma (33)
1 8 M C.46316-C C.14176-C. C.14176-C. C. 14176-C. C. 141	1309						delC;	37	alive	>25	ou	yes (37)	no	ou	none	
1	1309					2.2	delC;	36	alive	50-100	ОП	yes (36)	no	9	none	
1	1315		₩			p.Alac. c.536A>G; p.Tyr179Cys c.1187G:	3>A; p.Gly396Asp	99	alive		yes (66)	yes (69)	01	01	none	
1 B F C.5580-Sc, p. Pyt/1760ys c.2580-Sc, p. Pyt/1760ys c.2580-	1323		1			c.536A>G; p.Tyr179Cys c.1187G	3>A; p.Gly396Asp	33			01	yes (35)	no	ou	none	endometrial
1 1 1 1 1 1 1 1 1 1																carcinoma (54), benign skin tumor
1 8 M 6.5864-6c; p.ly1790ys c.5364-6c; p.ly1790ys c.3264-6c; p.ly1790ys c.3264-6	1334		1			c.643G>A; p.Val215Met c.884C>	>T; p.Pro295Leu	30		nultiple	yes (30)	yes (30)	multiple adenomas	00	none	ı
1	1338		—			c.884C>T; p.Pro295Leu c.884C>	>T; p.Pro295Leu	36	alive	50-100	no	yes (41)	01	no Ou	none	
1	1358					c.536A>G; p.Tyr179Cys c.536A>	>G; p.Tyr179Cys	40	alive		yes (48)	yes (49)	01	9	none	breast cancer (49)
B M C.14371.4499-bicKeds, by 1790s c.11471-bicKed; 37 alive multiple no yes (37) no none none no none no no	1358					c.536A>G; p.lyr1/9Cys c.536A>	>G; p.lyr1/9Cys	45		<40	yes (53)	yes (45)	00	00	none	
1 8 M 6.264-Sc; p.1y17260s 6.2636-Sc; p.1y17260s 6.2364-Sc; p.1y17260s 6.2364-Sc	1371		+			c.536A>G; p.Tyr179Cys c.1147di	delC;	37			No	yes (37)	ПО	00	none	
1	1372		1				1499delGGA;	37		nultiple	yes (37)	ves (37)	00	no	none	
1 8 M C56C-T; p.Ag130K C11377-0-K;							1480del									
1	1389		T.			0.7	delC;	43	alive	02-09	yes (43)	yes (44)	no	no	none	
2 B M. 6.5804-OG, Dyly1706ys, 6.1364-OG, Dyly1706ys, 6.1367-OG, Dyly1706ys, 6.13	1406		+			c.536A>G; p.Tyr179Cys c.1187G;	3>A; p.Gly396Asp	53	alive		yes (53)	OU.	unknown		unknown	
1 B M 6.5843-6; p.1y1719Ops 6.5364-6; p.1y1719Ops 6.3364-6; p.1y173Ops 6.1187G-3v; p.0y3964sp 44 alive some 26 yes (44) no unknown	1406					c.536A>G; p.Tyr179Cys c.1187G.	3>A; p.Gly396Asp	22	alive	50-100	no	yes (55)	no	ou	none	
2 B F G.536A-G; p.1y1796ys G.536A-G; p.1y1736ys G.5	1412					c.536A>G; p.Tyr179Cys c.536A>	>G; p.Tyr179Cys	44		numerous	yes (44)	yes (50)	no	ou	none	lipoma
1	1412					c.536A>G; p.Tyr179Cys c.536A>	>G; p.Tyr179Cys	34	alive	\ \ 2	no	unknown				endometrial
1 B M C.536A-G; D.YAT3GOS C.8334-3A-C C C C C C C C C C	,							G	-		000					carcinoma (47)
1 1 2 8 M 0.536k-G; D.My.179Oys 0.933+3A-C 2 4 4 4 4 4 4 4 4 4	1412					c.bbok. c.bbok.	oe; p.rytt/90ys	ર	DA I		(22)	2	UTIKITOWII		UTKTIOWIT	tumor (32), ovaria
1 1 2 8 M 0.2584-G; DiVIJT9Ops 0.11870-A; DiQh3G6Asp 44 alive some 26 yes (44) no unknown unknown unknown nuknown	1421		1			2,536A>G; p,Tvr179Cvs c,933+3	3A>C	52	alive		No.	No.	unknown	unknown	unknown	benign skin tumor (2
1 2 B F C.22GGA-G; p.Ty.179Oys C.1187G-A; p.Gly39GAsp A 1 alive 26 yes (44) no unknown	1451		₩			2.536A>G; p.Tyr179Cys c.1187G	3>A; p.Gly396Asp	49		ome	yes (49)	01	unknown	unknown	unknown	testical teratoma (28
1 B F C.7226-A; C.1187G-A; p.dy396Asp A5 alive 100-500 yes (45) yes (69) no no norm-in-in-in-in-in-in-in-in-in-in-in-in-in-	1451					c.536A>G; p.Tyr179Cys c.1187G	3>A; p.Gly396Asp	44	alive	26	yes (44)	OU.	unknown	unknown	unknown	benign endometrial
1 B F c.536A-G; p.1yd.79Oys c.1187G-A; p.Gy39GAsp 52 alive 50-80 no no unknown unknown unknown unknown 1 B F c.536A-G; p.1yd.79Oys c.1884C-Y; p.Pa023GLau 31 alive 50-60 yes (31) yes (31) no no no 1 B M c.536A-O; p.1yd.79Oys c.1187G-A; p.Gy39GAsp 58 alive yes (64) yes (50) unknown number of no unknown number of no unknown number of no	561		+			lGin	3>A; p.Gly396Asp	45	alive		yes (45)	yes (69)	0	OU.	none	breast cancer (60, 6) spinalioma (68),
1 B F C2904-Cit p1/y1/19/95 c.1187G-3-K p3/g96ksp 52 alive 50-b0 yes (31) yes (54) yes (51) normmer unrown 1 B M C536A-Cit p.1/y1/29Os c.1887G-3-K p.6/y36ksp 58 alive 50-b0 yes (64) yes (54) yes (50) unknown number of no norm control p1 B M C536A-Cit p.1/y1/29Os c.1187G-3-K p.6/y36ksp 58 alive 50-b0 yes (64) yes (54) yes (50) unknown number of no norm control p1 B M C536A-Cit p.1/y1/29Os c.1187G-3-K p.6/y36ksp 58 alive 50-b0 yes (64) yes (54) yes (50) inknown number of norm control p1 B M C536A-Cit p.1/y1/29Os c.1187G-3-K p.6/y36ksp 58 alive 50-b0 yes (64) yes (54) yes (50) inknown number of norm control p1 B M C536A-Cit p.1/y1/29Os c.1187G-3-K p3/g36ksp 58 alive 50-b0 yes (64) yes (54) yes (55) inknown number of norm control p1 B M C536A-Cit p.1/y1/29Os c.1187G-3-K p3/g36ksp 58 alive 50-b0 yes (64) yes (54) yes (55) inknown number of norm control p1 B M C536A-Cit p.1/y1/29Os c.1187G-3-K p3/g36ksp 58 alive 50-b0 yes (64) yes (64) yes (54) yes (65) yes			,					i		0						penign skin tumo
1 B M c.53dh-St; p.Tyr1790ys c.11870-N; p.Gly398Asp 58 aline 50-50 yes (64) yes (54) yes (50) unhown number of no hyperplastic from the control of the contr	1434		H +			c.536A>G; p.Tyr179Cys c.1187G	3>A; p.Gly396Asp	52	alive		no (24)	no 	unknown	unknown	unknown	
and the property of the proper	1401					c.536A>G; p.1yr1/9Cys c.884C>	>1; p.Prozesteu 3>4: p.Brozesteu	31	alive		yes (31)	yes (31)	no introven number of	0 0	none	
			4			Digital short shor	deconomic of the	3	2		(10) 526	(00) 506	hyperplastic		and histology	

Patient Index case no. (1)/relative		Center Gen	Gender	Mutation 1	Mutation 2	Age" at diagnosis	Cause and age ^a at death	Maximal polyp number colorectum	Colorectal cancer (age ^a)	Colorectal Gastroduodenoscopy No. and histology of Duodenal ancer (age*) duodenal polyposis cancer	No. and histology of duodenal polyposis	of Duodenal s cancer	No. and type of gastric polyps	Extracolonic tumor (age ^a at diagnosis)
1512	4 -	8 _	Σ u	c.536A>G; p.Tyr179Cys c.93	c.933+3A>C	40	alive	multiple	01 0	yes (40)	no	no	none	
				ne.				:	}	1				
	н	_	 Z	c.1214C>I; c.73 n Pro405I eu	c. /39 C>1; p.Arg24/X	8	alive	10-100	yes (48)	yes (47)	no	0	none	
96061	1	۷	ω.	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	36A>G; p.Tyr179Cys	41	CRC (44)	multiple	yes (41)	ou	unknown	unknown	unknown	
19045	1	LF		.Tyr179Cys	c.691-1 G>A	42	alive	10-50	no	ou	unknown	unknown		
19047	н	_	i L	c.1187G>A; c.11 p.Glv396Asp	c.1187G>A; p.Gly396Asp	33	alive	10-20	00	OU	unknown	unknown	unknown	
19047	1	LF	C)	-	c.1187G>A; p.Gly396Asp	40	alive	polyposis	ou	yes (60)	no	00	none	
	2	2	Σ.	p.Gly396Asp c.1187G>A: c.11	c.1187G>A; p.Glv396Asp	30	alive	1	2	01	unknown	unknown	unknown	
				ds										
	m	_	Σ.	c.1187G>A; c.11	c.1187G>A; p.Gly396Asp	38	alive	2	ou	OU	unknown	unknown	unknown	
	4	۷	ω		c.1187G>A; p.Gly396Asp	57	CRC (58)	sdílod	yes (57)	ou	unknown	unknown	unknown	
				ds	1000000	1								
	n	_	ئ ≥	C.IIS/G>A, C.II p.Glv396Asp	C.T.LO7 G.^A, p.Gly390ASp	2	allog	polyposis)es (10)	2	UIIKIIOMII	UIIKIIOMII	ULIKTIOWII	
19049	1	۷ ا	Σ.	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	36A>G; p.Tyr179Cys	46	alive	multiple	no	ou	unknown	unknown	unknown	bladder carcinoma (60),
														other benign tumors (62), benign skin tumor
	5	ν ν	Ω.	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	36A>G; p.Tyr179Cys	53	unknown (71)	100-1000	yes (53)	ou	unknown	unknown	unknown	
				c.536A>G; p.Tyd.79Gys c.536A>G; p.Tyd.79Gys	36A>G; p.Tyr179Cys		other cancer than CRC (74)	100-1000	yes (56)	yes (57)	2	0	none	carcinoma of the larynx (48), benign skin tumor (60), bladder
	4	ر د	Σ.	c.536A>G; p.Tyr179Gys c.536A>G; p.Tyr179Gys	36A>G; p.Tyr1.79Cys	20	accident (77)	100-1000	00	0	unknown	unknown	unknown unknown	prostate cancer (62), benign skin tumor (63)
				c.536A>G; p.Tyr179Cys c.933+3A>C	33+3A>C	51	alive	polyposis	yes (51)	no	unknown	unknown	unknown	
	7	ν	 M	c.536A>G; p.Tyr1.79Cys c.933+3A>C	33+3A>C	53	disease other polyposis than cancer (76)	polyposis	yes (53)	ОП	unknown	unknown	unknown	
	-	2	M	c.536A>G; p.Tvr179Cvs c.536A>G; p.Tvr179Cvs	36A>G; p.Tvr179Cvs	36	alive	>100	ou	no	unknown	unknown	unknown	
	7	_		c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	36A>G; p.Tyr1.79Cys	37	alive	М	01	yes (52)	unknown numberof no	ou Jo	none	
	e	۷		c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	36A>G; p.Tyr179Cys	44	alive	25-50	no	yes (61)	ou	OL OL	none	
19095	4	_	M C.	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	36A>G; p.Tyr179Cys	46	alive	numerous	ou	yes (50)	ou	ou 0	fundic gland	
		7		c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	36A>G; p.Tyr1.79Cys	40	alive	10-50	yes (40)	yes (50)	25 adenomas	2	polyp fundic gland polyn	
	_	2	M	c.536A>G: p.Tvr179Cvs_c.12	c.1214C>T: p.Pm405 eu		CRC (56)	30-100	ves (45)	ves (56)	1 adenoma	Nes	none	melanoma (30)
	1 0				214C>T; p.Pro405Leu	46		unknown	yes (46)	no on	unknown		unknown	(00)
	1	۷		c.536A>G; p.Tyr179Cys c.53	c.536A>G; p.Tyr179Cys	43		multiple	yes (43)	yes (63)	no	DI OI	none	benign skin tumor
	2	٧ _		c.536A>G; p.Tyr1.79Cys c.53	c.536A>G; p.Tyr179Cys	51			yes (51)	uo.	unknown	unknown	unknown	
	3	ر ا		c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	36A>G; p.Tyr179Cys	47	unknown (52)	09	no	ou	unknown	unknown	unknown	
		_ :		c.536A>G; p.Tyr179Cys c.1214C>T; p.Pro405Leu	214C>T; p.Pro405Leu	0		10-100	yes (50)	yes (62)	ou	OL .	none	
20090	0.4			c.536A>G; p.Tyr179Cys c.1214C>T; p.Pro405Leu	214C>T; p.Pro405Leu	ඉ ද	40)	few	yes (39)	OU .	unknown	unknown	unknown	
50176 50176	- 0			0.030A>G; p.1yr1/9Cys	1876-A; p.Gly390ASp	70 00	alive	200	9 6	yes (52)	0 %	2 2	none	
	4 F			c.536A>G; p.Tyr1.79Cys c.536A>G; p.Tyr1.79Cys	36A>G; p.Tyr179Cys	33	alive	50-100	yes (44)	yes (46)	2 2	2 2	20 fundic gland	benign skin tumor (46)
					:	!				•			polyps	
51545	,	_	ن ح	536A>G: D. IVr1/9Cvs c.11	147delC:	2	3/1/0	population	2	1000	2	2	0000	

(Continued)
Table 1.
Supplementary

:												I		
Patient Index case no. (1)/relative	Index case (1)/relative Center Gender	Center (Gender	Mutation 1	Mutation 2 d	Age ^a at diagnosis	Age at Cause and diagnosis age at death	Maximal polyp number colorectum	Colorectal Ga	astroduodenoscopy (age*)	Gastroduodenoscopy No. and histology of Duodenal (age*) duodenal polyposis cancer	Duodenal	No. and type of gastric polyps	Extracolonic tumor (agea at diagnosis)
52105	₽	_	Σ	c.536A>G; p.Tyr179Cys c.	c.536A>G; p.Tyr179Cys	43	_	polyposis	no	yes (68)	1 adenoma	0	none	basalioma (71)
52105	₽	_	Σ	c.536A>G; p.Tyr179Cys c.	c.1187G>A; p.Gly396Asp	33	alive	10-20	no	yes (50)		90	none	
52240	1	_	ш		c.1214C>T; p.Pro405Leu	22	CRC (58) p	polyposis	yes (58)	no	unknown	unknown	unknown	breast cancer (55)
90202	4	-	L	p.Pro405Leu	0.000 but T a .00 / A 0.00	ç	94	4	(00)	(40)				
02030	٠.	_ ـ	. :	C.330A/G; p.1yil/3Cys C.	COSON G, D. INITIACOS	5 6	allve	30-T00	yes (39)	yes (42)	≘ :	2 :	1016	0
22036	4	_	Σ	ds	3.3250.>1; p.Arg1091rp	25	URC (33)	00T-00	yes (52)	yes (DO)		2	rone	Denign skin tumor (50)
52654	1	_	Σ		s.1214C>T; p.Pro405Leu	37	CRC (39)	100-1000	yes (37)	no	nnknown	unknown unknown	unknown	
1000	c	-	L	na-	A DA AOS T D AOS	;				;				
52654	N	_	_	c.1214C>T; c. p.Pro405Leu	c.1214C>T; p.Pro405Leu	41	CRC (42) r	numerous	yes (41)	0	unknown	unknown unknown	unknown	
52689	₽	_	Σ	c.1171C>T; p.Gln391X c.1171delC; p.Gln391X	:.1171delC; p.Gln391X	36	unknown	110-120	no	OU	unknown	unknown unknown	unknown	
							cause/							
52699	1	_	Σ	c.536A>G; p.Tyr179Cys c.1147delC;	3.1147delC; p. Ala385ProfeX25	37	alive	10–100	OU	yes (37)	ou	9	none	
53029	1	٦	ш	c.536A>G; p.Tyr179Cys c.1214C>T; p.Pro405Leu	:.1214C>T; p.Pro405Leu	44	alive	10-100	no	yes (59)	no	9	1fundic gland	
													polyp	
53029	2	_	Σ	.Tyr179Cys	c.1214C>T; p.Pro405Leu	41		multiple	yes (41)	yes (42)			none	
53231	₩	_	ш	c.1187G>A; c. p.Gly396Asp	c.1187G>A; p.Gly396Asp	29	CRC (62) F	polyposis	yes (59)	0	unknown	unknown	unknown	
53276	1	_	Σ		c.1214C>T; p.Pro405Leu	48	alive	100-1000	yes (48)	yes (57)	yes	0	none	basalioma (58)
54092	-	-	ш	p.Gly396Asp c.1187G>A:	c.1187G>A: n.Glv396Asn	09	alive	<100	(O9) sex	9	IIIIknown	Inknown	unknown	
				sb										
54092	7	_	Σ	c.1187G>A; c.	c.1187G>A; p.Gly396Asp	24	alive	30-50	0	ou	unknown	unknown unknown	unknown	
54140	4	_	ш	pgg;	c.1227_1228dupGG;	42	alive	10-50	yes (42)	ou	unknown	unknown unknown	unknown	cervix carcinoma (27),
				s43	p.Glu410fs43									breast cancer (50)
54178	₩	_	ш	c.1187G>A; c. p.Gly396Asp	c.1214C>T; p.Pro405Leu	44	alive	50-100	yes (44)	yes (52)	OU	2	none	
54186	₩	_	ш	c.536A>G; p.Tyr179Cys c.	c.536A>G; p.Tyr179Cys	45	CRC (49) p	polyposis	yes (45)	01	unknown	unknown	unknown	basalioma (41)
54186	2	_	ш	c.536A>G; p.Tyr179Cys c.	c.536A>G; p.Tyr179Cys	43		20	yes (43)	yes (43)	yes		none	
54245	7	_	ш	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	:.536A>G; p.Tyr1.79Cys	54	unknown, 83	10-100	yes (54)	no	nnknown	unknown	unknown	breast cancer (76, 78),
														basalioma (63),
54245	2	_	ш	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	:.536A>G; p.Tyr179Cys	64	disease other		yes (64)	OU	unknown	unknown unknown	unknown	lung cancer (69)
							than							
54856	₽	_	ш	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	3.1187G>A; p.Gly396Asp	24	alive	10-100	OU OU	yes (55)	no	9	none	breast cancer both sides (50)
54856	7	_	ш	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	:.1187G>A; p.Gly396Asp	09		unknown	yes (61)	Ou			unknown	
54856	m	_	Σ	.Tyr179Cys	c.1187G>A; p.Gly396Asp	99	(89	numerous	yes (66)	u0	nown	unknown	unknown	
54962	₩	_	ш	c.1187G>A; c. p.Gly396Asp	c.1214C>T; p.Pro405Leu	41	alive	50-100	9	yes (47)	no n	2	none	
54962	2	_	ш	c.1187G>A; c.	c.1214C>T; p.Pro405Leu	51	alive	н	yes (51)	yes (55)	no	9	none	
55123	Ħ	_	ш	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	:.1187G>A; p.Gly396Asp	28	alive	30	yes (58)	yes (65)	no	9	fundic gland	benign breast
55247	+	_	ш	c.536A>G; p.Tvr179Cvs c.739 C>T; p.Arg247X	:.739 C>T: p.Arg247X		alive	50-100	ves (46)	ves (63)		90	polyps	(SS)
55356	₩	_	ш	c.1214C>T; c.	c.1147delC;	40	unknown (70) polyposis	olyposis	yes (42)	yes (58)	00	2	none	
				200000000000000000000000000000000000000										

no. (1)/relative Center Gender (1)/relative Center (1)/relative Ce	e G G G G G G G G G G G G G G G G G G G			Age* at Cau diagnosis age* (CRC) (45 CRC) (25 alive 24 alive 43 alive 67 alive 43 alive 64 alive 64 alive 64 alive 65 alive 64 alive 64 alive 64 alive 64 alive 64 alive 65 al	se and at death 45)	olyp	rectal r (age ^a) (45) (59) (49)	astroduodenosco) (age#) no no	Gastroduodenoscopy No. and histology of Duodenal (age*) duodenal polyposis cancer no unknown no unknown no innknown	s cancer unknown t	No. and type of gastric polyps unknown unknown unknown unknown	Extracolonic tumor (age, at diagnosis)
				ilignosis aggi 55 alivi 65 alivi 66 alivi 67 alivi 68 alivi 69 alivi 69 alivi 69 alivi 60 alivi	==	35 35 >20 0-25 >100	yes (45) yes (59) yes (49)	(age ^a) no no	duodenal polyposis unknown unknown	nknown unknown	gastric polyps unknown unknown unknown	(age® at diagnosis)
	ΣμΣΣΣΣΣΣ μ μμ Σ ΣΣμΣΣ Σ		6.1387-X-Y, DAY 1790-S 6.11870-X, DAY 290-Ses-Ses-Ses-Ses-Ses-Ses-Ses-Ses-Ses-Ses		45)	35 >20 20-25 tiple tiple	yes (45) yes (59) yes (49)	Q Q Q	unknown unknown		unknown unknown unknown	
	L Z Z Z Z Z L LL Z Z Z L Z Z Z		a.1187Ca-k, polya986ksp. a.1187Ca-k, polya96ksp. a.1187Ca		,	>20 20–25 tiple tiple tiple	yes (59) yes (49)	e e	unknown		unknown unknown	
	22222 u uu 2 22u22 2		c.11876-A, p. 0A/9364sp c.13876-A, p. 0A/9364sp c.13876-A, p. 0A/9364sp c.13876-A, p. 0A/9364sp c.1386-C, p. 1A/1790ys c.1386-C,	##### # B # # ##### # # # # # # # # # #	,	20–25 tiple ttiple >100	yes (49)	DO.	ıınknown		unknown	
	2 2 2 2 2 L L L Z 2 2 L L Z 2		c.11870-x, p.0k396ks c.536k-c, p.0k396ks c.536k-c, p.1k1790,s c.11870-x, p.0k396ks c.11870-x, p.0k396ks c.11870-x, p.0k396ks c.11470-c, p.0k385rok25 c.11470-c, p.0k385rok25 c.11470-c, p.0k385rok25 c.136k-c, p.1k1790,s c.236k-c, p.1k1790,s c.236k-c, p.1k1790,s c.236k-c, p.1k1790,s c.236k-c, p.1k1790,s c.236k-c, p.1k1790,s c.11870-x, p.0k396ks c.11870-x, p.0k396ks		,	tiple tiple >100			direction			
	2222 u uu 2 22u22 2		c.11870-X, p.0)49364sp c.11870-X, p.0)49364sp c.11870-X, p.0)49364sp c.11870-X, p.0)49364sp c.11870-X, p.0)49364sp c.13870-X, p.0)49364sp c.13870-X, p.0)49364sp c.13870-X, p.0)49364sp p.1470-Se c.13880-C, p.147190-S		,	tiple >100	2	no	unknown	unknown	unknown	
663551 1 1 6 663551 1 1 6 66566 2 1 6 6666 1 1 6 6 6641 1 1 6 67137 1 1 6 67139 1 6 67139 1 1 6 67139	2 2 2 L LL 2 2 2 L 2 2 2		6.1387-6. pV4790;s 6.1387-8. p.049364sp 6.11876-8. p.049364sp 6.13876-8. p.049364sp 6.13876-8. p.047364sp 6.1388-6. p.14730;s 6.147046; p.043887048.25 6.1388-6. p.14730;s 6.1388-6. p.14730;s 6.1388-6. p.14730;s 6.1388-6. p.14730;s 6.1388-6. p.14730;s 6.1388-6. p.14730;s 6.1388-6. p.14730;s 6.1388-6. p.14730;s 6.1388-6. p.14730;s 6.1388-6. p.14730;s		9. 9.	>100	ou	yes (48)	no	no n	none	
565666 1 1 565666 2 1 1 56566 2 1 1 1 1 1 1 1 1 1	22 u uu 2 22u22 2		c.1187G-A; p.0ky396ksp c.1187G-A; p.0ky396ksp c.1387G-A; p.0ky396ksp c.1387G-A; p.0ky396ksp c.1377G-B; p.0ky387G-RSZ5 c.1377G-B; p.1478G-B; p.1478G-B; p.1478G-B; c.1384-G; p.1479G-B; c.1384-G; p.1479G-B; c.1384-G; p.1479G-B; c.1384-G; p.1479G-B; c.1387G-A; p.0ky396ksp c.1187G-A; p.0ky396ksp		e, e	007	no	yes (36)	yes	_	none	benign skin tumor
56641 1 1 567135 1 1 1 57735 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Σ ι ιι Σ ΣΣιΣΣ Σ		c.1187G-N; p.0y396ksp c.1187G-N; p.0y396ksp c.1187G-N; p.0y1790ys c.11470elC; p.0x38870elX25 c.11470elC; p.0x38870elX25 c.1358A-N; p.1y1790ys c.1358A-N; p.1y1790ys c.1387G-N; p.0y390ksp c.1387G-N; p.0y390ksp c.1387G-N; p.0y390ksp			>100	yes (67)	yes (67)	ou	01	none	
56641 1 1 1 5735 1 1 1 57337 1 1 1 57246 1 1 1 1 57249 2 1 1 57249 3 1 1 57249 3 1 1 1 57308 1 1 1 57308 1 1 1 57308 1 1 1 57308 1 1 1 1 57308 1 1 1 1 57308 1 1 1 1 57308 1 1 1 1 57308 1 1 1 1 57308 1 1 1 1 1 57308 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	ц μ Σ ΣΣμΣΣ Σ		c.1187G-A. p.04396Asp c.536A-Gc, p.14790ys c.11470elC; p.0438570elX25 c.11470elC; p.0438570elX25 c.11470elC; p.047170ys c.536A-Cc, p.14770ys c.536A-Cc, p.14770ys c.536A-Cc, p.14770ys c.136A-Cc, p.14770ys c.136A-Cc, p.14770ys c.136A-Cc, p.14770ys c.136A-Cc, p.14770ys c.136A-Cc, p.14770ys		unknown if		unknown	01	unknown	unknown	unknown	
57135 1 L 57135 1 L 57139 1 L 57246 1 L 57249 2 L 57249 3 L	. μα Σ ΣΣαΣΣ Σ		6.5364-C; p.Tyd.790/s 6.5364-C; p.Tyd.790/s 6.1470elc; p.AussStreek25 6.1470elc; p.AussStreek25 6.5384-C; p.Tyd.790/s 6.5384-C; p.Tyd.790/s 6.1367-C; p.Tyd.790/s 6.1367-C; p.Tyd.790/s 6.1367-C; p.Tyd.790/s		deceased	10_50	ves (43)	ves (53)	9	2	eucon	henian endometrial
57135 1 L 57137 1 L 57139 1 L 57246 1 L 57249 2 L 57249 3 L 57249 1 L	μα Σ ΣΣαΣΣ Σ	6.536A-G; p.ly179Oys 6.536A-G; p.ly179Oys 6.1387Ca-A; p.08/396Asp 6.536A-G; p.ly179Oys 6.536A-G; p.ly179Oys 6.136A-G; p.ly179Oys 6.1187Ca-A; p.08/390Asp 6.536A-G; p.ly179Oys 6.536A-G; p.ly179Oys 6.536A-G; p.ly179Oys	c.538A-G; p.Jyr179Qs c.11470Bc; c.11470Bc; c.1470Bc; c.1470Bc; c.1370Bc; c.1370Bc; c.1370Bc; c.138A-G; p.Jyr179Qs c.138A-G; p.Jyr179Qs c.138A-G; p.Jyr179Qs c.138A-G; p.Jyr179Qs		2	200	Jea (45)	Jea (22)	2		2	tumor (57)
57137 1 L 57139 1 L 57246 1 L 57249 1 L 57249 2 L 57249 3 L 57308 1 L	L Z ZZLZZ Z	c.536A-G; p.1yr179Cys c.1187G-A; p.10/8958As p.10/8958As c.536A-G; p.1yr179Cys c.536A-G; p.1yr179Cys c.536A-G; p.1yr179Cys c.1187G-A; p.10/39GAsp c.536A-G; p.1yr179Cys	c.11470elc; p.Au3856rois25 c.11470elc; p.Au3856rois25 c.11470elc; p.Au3856rois25 c.13634-Ce; p.Yu1790ys c.13634-Ce; p.Yu1790ys c.13634-Ce; p.Yu1790ys c.1367-Xr; p.0y3396xsp c.1367-Xr; p.0y3396xsp		CRC (49)	>25	yes (46)	No	unknown	unknown	unknown	basalioma (44)
57139 1 L 57246 1 L 57249 1 L 57249 2 L 57249 3 L 57308 1 L	Σ ΣΣμΣΣ Σ	c.1187G-A; p.69/396ksp c.536k-G; p.174790ys c.536k-G; p.1747190ys c.536k-G; p.174790ys c.1187G-A; p.69/396ksp c.536k-G; p.174790ys	p.Alastschock\Co. Li.77de(C. Li.77de(C. Li.28de-Cc. Li.28de-Cc. Li.77de(C. Li		, e,	36	yes (21)	yes (28)	no	00	none	
57139 1 L 57246 1 L 57249 1 L 57249 2 L 57308 1 L	Σ ΣΣμΣΣ Σ	c.1381C-A; c.538A-C; p.ly4129Cy c.538A-C; p.ly4129Cy c.538A-C; p.ly4129Cy c.538A-C; p.ly4129Cy c.1381C-A; p.Gy39GAsp c.538A-C; p.ly4179Cys	c.1147616; c.5364-06; p.1v1790; c.5364-06; p.1v1790; c.5364-06; p.1v1790; c.5364-06; p.1v1790; c.11870-A; p.0k70968; c.13870-A; p.0k70968;									
57246 1 L 57249 1 L 57249 2 L 57249 3 L 57308 1 L	ΣΣπΣΣ Σ	p.0(4)390Asp c.538A-Ci, p.1y/190ys c.536A-Ci, p.1y/1790ys c.538A-Ci, p.1y/1790ys c.1187G-A; p.Ciy396Asp c.538A-Ci, p.1y/1790ys	p. Aus28Ports/25, c.536A-G; p.1yr1790ys c.536A-G; p.1yr1790ys c.536A-G; p.1yr1790ys c.536A-G; p.1yr1790ys c.1187G-A; p.Gly396Asp c.1187G-A; p.Gly396Asp c.536A-G; p.1yr1790ys	त्रे के त्रे ते	ve.	10-50	yes (42)	yes (61)	no	no n	none	
57246 1 L 57249 1 L 57249 2 L 57249 3 L 57308 1 L	ΣΣμΣΣ Σ	c.536k-5(; p.lyr1790ys c.536k-6; p.lyr1790ys c.536k-6; p.lyr1790ys c.138k-6; p.lyr1790ys p.Gly396ksp c.536k-6; p.lyr1790ys	c.5584>G; p.fy1790ys c.5364>G; p.fy1790ys c.5364>G; p.fy1790ys c.1437G>A; p.fy1790ys c.1437G>A; p.fy1790ys									
57249 1 L 57249 2 L 57249 3 L 57308 1 L	ΣπΣΣ Σ	c.536A-G; p.Jy1790ys c.536A-G; p.Jy1790ys c.1187G-A; p.Gly396Asp c.536A-G; p.Jy1790ys	c.536A>G; p.Jyd.790/s c.536A>G; p.Jyd.790/s c.1187G>A; p.Gy396Asp c.536A>G; p.Jyd.790/s	ing dispersion of the	ve.	10-100	yes (65)	yes (65)	2 adenomas		none	
57249 2 L 57249 3 L 57308 1 L	μΣΣ Σ	c.536A>G; p.1yr1790ys c.536A>G; p.1yr1790ys c.1887G>A; p.Gly396Asp c.536A>G; p.1yr1790ys	c.536A>G; p.1y1790ys c.536A>G; p.1y1790ys c.1187G>A; p.Gly396Asp c.536A>G; p.1y1790ys	में हैं में		polyposis	yes (49)	yes (59)	U0	00	none	esophagic cancer (59)
57249 3 L 57308 1 L	ΣΣ Σ	c.536A>G; p.Tyr1790ys c.1187G>A; p.Gly396Asp c.536A>G; p.Tyr1790ys	c.536A>G; p.ľyd.790ys c.1187G>A; p.Gly396Asp c.536A>G; p.ľyd.790ys	ali di		multiple	yes (49)	yes (49)	no		none	
57308 1 L	ΣΣ	c.11876>A; p.Gly396Asp c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp c.536A>G; p.Tyr1.79Cys	gi ili		numerous	yes (52)	yes (58)	no		none	
	Σ		c.536A>G; p.Tyr179Cys	a <u>ri</u>	disease other	>15	no	no	unknown	unknown	unknown	
	Σ		c.536A>G; p.Tyr179Cys	ali	than cancer (47)							
57449 1 L						>100	yes (45)	yes (58)	по	01	none	sebaceons gland
												adenoma (68), benign skin
57591 1 L	Σ	c.1214C>T;	c.933+3A>C	40 CR	CRC (41)	50-100	yes (40)	OU.	unknown	unknown unknown	unknown	
00000	ı	p.Fr04USLeu	-			,						
3/3/6 I L	_	6.536A>'G'; p.1yf1/9Cys 6.1Z14C>1; p.Ff04U5Leu	c.izi4c>i; p.Pro4ubleu	64 din	unknown if deceased	1	2	2	unknown	unknown	UNKHOWN	
58746 1 L	ш	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	27 alive	, e	30-40	ou	yes (29)	no	no n	none	
60322 2 L	Σ	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	64 alive	ve		yes	. 01	unknown	nown	unknown	
60322 3 L	ш	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	55 alive	,e		yes	ou	unknown	unknown	unknown	
60406 1 L	Σ	c.1437_1499delGGA; c	c.1437_1499delGGA;	49 alive	ve	10-100	yes (51)	no	unknown	unknown	unknown	
			p.Glu480del									
60406 2 L	Σ	elGGA;	c.1437_1499delGGA;	'n	unknown if	30	no	yes (50)	no	01	fundic gland	benign skin tumor (53)
	:		p.Glu480del	i	deceased						sdklod	
62512 1 L	Σ:		C.1214C>I; p.Pro4U5Leu	29 allive	9 :	30-40	OU :	OU	unknown	uwou	unknown	benign skin tumor (38)
62805 1 L	Σ	c.536A>G; p.1yr1/9Cys c.536A>G; p.1yr1/9Cys	c.536A>G; p.1yr1/9Cys	63 alive	ě	10-100	ou Ou	yes (67)	5 adenomas	0	fundic gland polyps	
65739 1 L	Σ	c.536A>G; p.Tvr179Cvs c.925C>T; p.Arg309Cvs	c.925C>T; p.Arg309Cvs	63 alive	e/.	10-20	01	ves (58)	ou	01	none	
67143 1 L	ш	c.536A>G; p.Tyr179Cys c	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	61 alive	, e	20-50	yes (61)	yes (70)	no		none	benign skin tumor (54)
67143 2 L	Σ	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	fun	unknown if		unknown	OU	unknown	unknown	unknown	
,	:		000000		deceased	·	ŝ					
) H	Σ μ	c.536A>G; p.Tyr1.79Cys c	c.536A>G; p.lyr179Cys c.1187G>A; p.Gly396Asp	31 alive	e ve	N F	yes (36)	ou c	unknown	unknown	unknown	benign skin tumor (33)
1 6	ш	c.3308/d, p.1yit130ys	C.TISTG/A, p.diyasonap		p g	H 49/	2 2	110 vec (35)	unknown		unknown	henidn breast
4	-	Jen	2000		D	2	2)ea(diriowin		diniowii	tumor (22)
2 2 C	ш		c.933+3A>C	41 alive	9/	20	no	unknown				(42) (47)
		ds										
2 3 C	ш		c.933+3A>C	57 alive		unknown	yes (57)	unknown				
	ı	ds										
2 4		C.118/G>A; C	C.933+3A>C	allve		multiple	ou	uo	unknown	unknown unknown	unknown	ovarian cancer
2	Σ	p.cdyccomsp c 1187G>∆.	J<₹34>3	alive		a number of	2	IIIknown				other henian tumors
		n.Glv396Asn		3		nolvos	2					200000000000000000000000000000000000000

Supplementary Table 1. (Continued)

1 C M CENTROLE LANGUAGE	H H H H H H H H H H M M H H M M M H M H	438G>T; p.Glu480X d3cA-G; p.Tyr1790ys g3cA-G; p.Tyr1790ys g3cA-G; p.Tyr1790ys g3cA-G; p.Tyr1790ys g3cA-G; p.Tyr1790ys city326Asp gacA-G; p.Tyr1790ys g3cA-G; p.Tyr1790ys g3cA-G; p.Tyr1790ys g3cA-G; p.Tyr1790ys g3cA-G; p.Tyr1790ys g	44390 - T. D. 4800					(40)				
1 C C C C C C C C C		438G>T; p.Glu480X 36A>G; p.Tyr1790ys 36A>G; p.Tyr1790ys 36A>G; p.Tyr1790ys 36A>G; p.Tyr1790ys 187G>A; p.Gly396Asp	4 4 3 9 C - T - D G I - 4 9 C V			40-50		100 (40)				
1	тинни ни пи оминоманом и о инночомаюноми и н мгжжж гх хх гг хххххгх х г гг хххххгг хгхг х х	36A>G; p.1yr179Cys 36A>G; p.1yr179Cys 36A>G; p.1yr179Cys 36A>G; p.1yr179Cys 187C>A; p.Gly39GAsp 36A>G; p.1yr179Cys	C. 14000/ 1. D.GIG+00A	51	alive	1	no	Ves (46)	no		one	
1 C M CANOLOGY M M M M CANOLOGY M M M M M M M M M		36A-S; p.Tyr1790ys 36A-S; p.Tyr1790ys 36A-S; p.Tyr1790ys 187G-A; p.Gy396Asp 36A-S; p.Tyr1790ys	c 1187G>A: n Glv396Asn	47	alive	25-30	ves (47)	ves (50)	00		one	
1 C M CARRELLO DATA TO A		364>6; p.1y11790ys of 364>6; p.1y1790ys of 364>6; p	0.1101 d. n. p. dj. 200 m.	- 0	o di di	2007	100 (11)	(oc) col	2		2	
1	NN LN NA CENTRENT NE CENTRE NE CENTR	36A>G; p.Tyr179Cys of 36A>G; p.Tyr179Cys of 36A>G; p.Tyr179Cys of 187G>A; of 187G>A; of 36A>G; p.Tyr179Cys of 36A	C.336A~G, p.1yt1/3cys	20	allve	TOO	yes (DT)	ULIKITOWII				
1	NN LN NN LLNLNNALN H N HHHNHNANANHNHH H H	364>G; p.Tyr179Cys o 187G>A; p.Gly396Asp 36A>G; p.Tyr179Cys o	c.1187G>A; p.Gly396Asp	47	alive	20-50	no no	00	unknown		nknown	
1	 н н н н н н н н н н н н н н н н н н н	187G>A; p.Gly396Asp 36A>G; p.Tyr179Cys	c.536A>G; p.Tvr179Cvs	41	alive	156	no	ou Ou	unknown	unknown	nknown	
1	. HH HH QWHHQW4HQW H Q HHHQHQW4WHQHH H H	p.Gly396Asp 36A>G; p.Tyr179Cys o	0 1187G>4: n Glv396Aen	62	alive	70	(C9) son	uwowanii				
1 C M CASSIN-CAP PAPILY PAP	 нн <li< td=""><td>p.ciyaadasp 36A>G; p.Tyr179Cys</td><td>devocation of the protection</td><td>1</td><td></td><td>2</td><td>100 (05)</td><td></td><td></td><td></td><td></td><td></td></li<>	p.ciyaadasp 36A>G; p.Tyr179Cys	devocation of the protection	1		2	100 (05)					
1		36A>G; p.lyr1/9Cys		i		;						
1	 ■ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ □		c.389-1G>A	26	alive	14	00	unknown				
1	N	36A>G; p.Tyr179Cys o	c.1187G>A; p.Gly396Asp	48	unknown	<100	no Ou	unknown				
1	HH 000HH0004H000 H 0 HHH0H004DH0HHH H H				cause/							
1 C M C125C-A-p (Judicol					age							
1	44 0044004400 4 0 4440400404040 0 0		0.342C>A: p. Tord 0.4X	ŗ.	- Pr	132	vae (F1)	Mae (55)	0		900	
1	 ■ 000000000000000000000000000000000000	120/A, p.191104A	COTEC/A, p.19/104A	T I	allive	704	(TC) Sak	yes (00)	2		910	
1	\[VOM H \q	438G>T; p.Glu480X	c.1438G>T; p.Glu480X	37	CRC (38)	>25	yes (37)	yes (37)	yes;		one	
1									number/histology			
	0000000000 0 0 000000000000 0 0 0 0 0								unknown			
1	V 0 1 1 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1	4200 T Ol.:400X	4 4000× T = Ol.: 4000	*		440		and and and				
1		4366 > 1; p.GIU460A	C.1435G/71; p.GIU45UA	44	allive	T43	DII O	UNKNOWN				
1 C M C3284-C6, p1/471590, c118176-A, b0/3695849 S alive S A	144004400 4 2 4440400404040 4 4 4 6 6 6 6 6 6 6 6 6 6	438G>T; p.Glu480X o	c.1438G>T; p.Glu480X	36	alive	120	yes (36)	unknown				
1	T N N N N N N N N N N N N N N N N N N N		c,536A>G; p.Tvr179Cvs	45	alive	>10	OL	01	unknown	unknown	nknown	
1	. X X X X L X X X L L X X X X L L X L X	364>6: p Tyr1790/g	0.1187G-A: p.Glv306Asp	73	aliva	c	Vac (43)	(AR)	9		900	
2 C M CASSIGN-Ce, Interval Color C	N 0 4 4 9 8 0 4 4 4 4 4 4 8 4 8 4 8 4 8 4 8 4 8 4	Social prigitations	devocation of the control	2 6	o i	0 ,	(2)	Jes (40)			2 .	
3 CM R. 2528A-C.G. PLYT/TOOPs CLIERIOR CALA DOR/SSORAGE GRC (4.7) multiple yes (4.5) no unknown	044900 H O 444944044044 H F	36A>G; p.lyr1/9Cys	c.1187G>A; p.Gly396Asp	53		>100	yes (b1)	ou	unknown		nknown	
4 C M CASSIDA-Sig PLYTTOONS LIRISTOCA-N, Doly-SidSkips GRC (43) unknown yes unknown unknown <td>4 H A B B B B B B B B B B B B B B B B B B</td> <td>36A>G; p.Tyr179Cys (</td> <td>c.1187G>A; p.Gly396Asp</td> <td></td> <td></td> <td>nultiple</td> <td>yes (45)</td> <td>no</td> <td>unknown</td> <td></td> <td>nknown</td> <td></td>	4 H A B B B B B B B B B B B B B B B B B B	36A>G; p.Tyr179Cys (c.1187G>A; p.Gly396Asp			nultiple	yes (45)	no	unknown		nknown	
1 C M C32804-Cg InVITYTOON CLISTON, LORGISCARD 49 alive E0-LON m no no <th< td=""><td></td><td>36A>G: n Tvr179Cvs</td><td>c 1187G>A: n Glv396Asn</td><td></td><td></td><td>nknown</td><td>SdV</td><td>Inknown</td><td></td><td></td><td></td><td></td></th<>		36A>G: n Tvr179Cvs	c 1187G>A: n Glv396Asn			nknown	SdV	Inknown				
1 C M C.3364-Ce, p.1y1790s C.11870-A. G RC(47) Description	4 0 0 4 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	2004-10 - T-4200-1	44070 A = 01,000A==	ç	î	400	2					
2 C F C5568-56; p.Jy4750-s. cl.1876-3-k. p.6j-396-kg. 51 cesed-66; p.Jy4750-s. cl.1876-3-k. p.6j-396-kg. 51 multipoe no mu	N 0	soa>'d; p.lyr⊥/ 9cys (C.T.Lo./ G.>A; p.Giy390ASp	1		OOT-OG	OII	OI.	Urikriown		IIKDOWII	
3 C M 4.5584-5G; p.1y4790ys c.1187G-Ak GRC (47) 2 addenomas in pres (46) no unknown unknown <td>N H N HHHNHNM40HNHH H H</td> <td>36A>G; p.Tyr179Cys o</td> <td>c.1187G>A; p.Gly396Asp</td> <td>21</td> <td></td> <td>nultiple</td> <td>00</td> <td>no</td> <td>unknown</td> <td></td> <td>nknown</td> <td></td>	N H N HHHNHNM40HNHH H H	36A>G; p.Tyr179Cys o	c.1187G>A; p.Gly396Asp	21		nultiple	00	no	unknown		nknown	
1 C F Catalogo	H O HHHOHOO 4 10 HOHH H H	36A>G; p.Tyr179Cys (c.1187G>A; p.Gly396Asp	46		adenomas in	yes (46)	unknown				
1 C M C1187G>A, C C1057G>A, C C1	1					resection						
1 C F Caraba-Cap, part 1790; a caraba-			Gln338X	49		ultiple	9	9	inknown	unknown	nknown	
2 C F C.12767-A. Districtions of the parameter of the par	0 000000000000000000000000000000000000	6		!			!					
1 C F C.5384-Sc p.147190-s C.4561-Sc p.147190-s S. Sc p. C.467 C.467 S.468 S.46 D. C.467 C.467 S.468 S.46 D. C.467 C.468 S.46 D. C.467 D. C.	N HHHUHUN40040HH H H	de		ě	000		-					
1 C F G.5384-C.G D.YAT19Oys G.53	H H H M H M M M M M M M M M M M M M M M		GIN338A	200	CRC (50)	ET.	(nc) sak	UNKNOWN				
1 C F G.5384-S.C p. Ny1790ys G.5384-C.C p. Ny		p.Gly396Asp										
1 C F C E C C C C C C C C	H H O H O W 4 W H O H H H H H H H H H H H H H H H H H	36A>G; p.Tyr179Cys (c.536A>G; p.Tyr179Cys	38		nultiple	yes (38)	no	unknown		nknown	
1	14 0 4 0 0 4 0 4 0 4 4 4 4 4 9 9 9 9 9 9	364>G: n Tvr179Cvs	c 1518+2T>C	41		nultiple	ves (41)	Ou.	inknown		nknown	breast cancer (71)
1	4 V H V W 4 W H W H W H W H W H W H W H W H W H		0.1.429C\T: p.Cl::.400V	Q.				(40)	0		000	honida ckin tumor (EE)
2 C M C.3126-2A-R, D/HGMA C.31436-2A-R, D/HGMA C.3146-2A-R, D/HGMA	N H W W 4 W H W H H H H H H H H H H H H H		C.T.+30d/l, p.diu+60A	Ť	allac	2002	2	yes (+3)	2		25	Delligii skiii tuliidi (33)
1 C M 6.3120-X-b, Phytokk	X X L L X L X L X L X L X L X L X L X L		C.1438G>1; p.Glu480X		unknown (47) L	nknown	unknown	unknown				
2 C M CATACO-A DIVIDIDAY CALCASTOR—A PUTLOAX CALCACA DIVIDIDAX CALCACACA DIVIDIDAX CALCACACACA DIVIDIDAX CALCACACACACACACACACACACACACACACACACACA	V W 4 W H V H H H H H H H H H H H H H H H H H		c.312C>A; p.Tyr104X	62	alive	>100	yes	yes (63)	no		one	
3 C F AZIZZZZ-A, LIVITAGA 38 alle >100 no unknown	00400000 0 0		c.312C>A; p.Tvr104X	22	alive	>12	ves (59)	01	unknown		nknown	
1			c 312C>A: n Tvr104X	38	alive	>100		00	IInknown		nknown	
1	1 M H M H M H H H		- 24 20 A - Tind 0 48	9 6	2 1	0		2 1				
5 C M. GABOA-SE, PLYINGMAR, GABOA-SEA, BUTLANGMAR, ASTACA-SEA, BUTLANGMAR, BUTLAN	N		C.SLZC>A; p.1yr104A	04	allive		UNIKHOWH	01	UNIKHOWII		IIKNOWII	
1 C F 6.2584-C6, p.14719C9s 6.2584-C6, p.14719C9s 5.35 alive 10-50 yes (45) yes (45) no none none no none no none no none no none no none no none none no none no none none no no none no	. X . X . X . X		c.312C>A; p.Tyr104X	46	alive	>100	0	u0	unknown		nknown	
2 C M CASSON-Co put/1790ye CAS	N N N N N N N N N N N N N N N N N N N		c.536A>G; p.Tyr179Cys	32	alive	10-50	yes (45)	yes (49)	no		one	
1 C F 6.5943-G; p.My179Oys C.1187C3-X; p.Gly39GAsp G G CPC (F9) > 100 yes (F5) unknown introversity of the c.1438C3-T; p.Glu480X C.1438C3-Y; p.Glu480X C.1	H H H H	36A>G: p.Tvr179Cvs	c.536A>G; p.Tvr179Cvs	23	CRC (53)	17	ves (53)	ves (53)	2		one	
1		364 > G. p. Tyrd 790 / e	0.11876 A. D.GN396Asp	S. C.	(69)	/400	, noe (6E)	umouduii				
1 C M 6.14360-7; Putidation, 6.14360-8; putidos 6.14870-7; putidos 6.14870-7	S S S	ASSOCIATION ASSOCI	4 4000 T - 01.4000	9 6	(00) 000	0 0 1	(20)	100			and the section of	1
1 C M G.2384-CG. D.M.179Cos c.1187C3-A, D.M.2986ks	1 T		C.1438G > 1; p.GIU48UA	00	CRC (69)	OCT	(co) sak	(co) sak	10		untiple polyps,	kidney cysts
1 C M C.187G-N; AsnZ38Ser So alive multiple small sessile yes (50) no unknown unknown unknown unknown no L.588-N; L	0 0										histology	
1 C M c.18767-b.k. Asn.238Ser 50 alive multiple snall sessile yes (50) no unknown unknown unknown unknown 1 C M c.538A-c6, p.ly47390s c.1187G-xb, p.dy3386ksp 65 alive polyps po no unknown unknown unknown 1 C M c.538A-c6, p.ly47390s c.1187G-xb, p.dy3386ksp 45 alive Fo no unknown unknown 3 C F c.538A-c6, p.ly47390s c.1187G-xb, p.dy3386ksp 45 alive Fo no unknown unknown 4 C M c.538A-c6, p.ly47390s c.1187G-xb, p.dy3386ksp 41 alive Fo no unknown no 4 C M c.538A-c6, p.ly47390s c.1187G-xb, p.dy3386ksp 41 alive Fo yes (44) unknown	7 C C										unknown	
C M	E ≥		Asn238Ser	20		nultiple small sessile	ves (50)	00	unknown	unknown	nknown	benien skin tumor (50)
1 C M c.358A-CG, p.Mr/19Qs, c.1187G-A, p.Gly39Gksp 65 alive propps yes (65) no unknown unknown 1 C M c.358A-CG, p.Mr/19Qs, c.1187G-A, p.Gly39Gksp 45 alive 60-75 no unknown unknown 3 C F c.358A-CG, p.Mr/19Qs, c.1187G-A, p.Gly39Gksp 45 alive 100 no unknown 4 C M c.358A-CG, p.Mr/19Qs, c.1187G-A, p.Gly39Gksp 41 alive frw no unknown 5 C M c.358A-CG, p.Mr/19Qs, c.1187G-A, p.Gly39Gksp 44 disease other 76 yes (44) unknown	0)		polyme	(20)					0
1 C M 6.2564-Cg, PLYT-959, e.1.187G-A, p.6/3968-pp 53 alive numerous yes(5) no unknown unknown 2 C M 6.2584-Cg, p.1/47199, e.1.187G-A, p.6/3968-pp 45 alive few 60-75 no unknown unknown 2 C M 6.2584-Cg, p.1/47199, e.1.187G-A, p.6/3968-pp 45 alive few 7-100 no unknown 4 C M 6.2584-Cg, p.1/47190, e.1.187G-A, p.6/3968-pp 41 alive few 7-100 no unknown 5 C M 6.2584-Cg, p.1/47190, e.1.187G-A, p.6/3968-pp 44 disease other 76 yes (44) unknown 4 H H G 6.2584-Cg, p.1/47190, e.1.187G-A, p.6/3968-pp 44 disease other 76 yes (44) unknown 4 H H G 6.2584-Cg, p.1/47190, e.1.187G-A, p.6/3968-pp 44 disease other 76 yes (44) unknown 4 H H G 6.2584-Cg, p.1/47190, e.1.187G-A, p.6/3968-pp 44 disease other 76 yes (44) unknown 4 H H G 6.2584-Cg, p.1/47190, e.1.187G-A, p.6/3968-pp 44 disease other 76 yes (44) unknown 4 H H G 6.2584-Cg, p.1/47190, e.1.187G-A, p.6/3968-pp 44 disease other 76 yes (44) unknown 4 H H G 6.2584-Cg, p.1/47190, e.1.187G-A, p.6/3968-pp 44 disease other 76 yes (44) unknown 4 H H G 6.2584-Cg, p.1/47190, e.1.187G-A, p.6/3968-pp 44 disease other 76 yes (44) unknown 4 H H G 6.2584-Cg, p.1/47190, e.1.187G-A, p.6/3968-pp 44 disease other 76 yes (44) unknown 4 H H G 6.2584-Cg, p.1/47190, e.1.187G-A, p.6/3968-pp 44 disease other 76 yes (44) unknown 4 H H G 6.2584-Cg, p.1/47190, e.1.187G-A, p.6/3968-pp 44 disease other 76 yes (44) unknown 4 H H G 6.2584-Cg, p.1/47190-pp 44 disease other 76 yes (44) unknown 4 H H G 6.2584-Cg, p.1/47190-pp 44 disease other 76 yes (44) unknown 4 H G 6.2584-Cg, p.1/47190-pp 44 disease other 76 yes (44) unknown 4 H G 6.2584-Cg, p.1/47190-pp 44 disease other 76 yes (44) unknown 4 H G 6.2584-Cg, p.1/47190-pp 44 disease other 76 yes (44) unknown 4 H G 6.2584-Cg, p.1/47190-pp 44 disease other 76 yes (44) unknown 4 H G 6.2584-Cg, p.1/47190-pp 44 disease other 76 yes (44) unknown 4 H G 6.2584-Cg, p.1/47190-pp 44 disease other 76 yes (44) unknown 4 H G 6.2584-Cg, p.1/47190-pp 44 disease other 76 yes (44) unknown 4 H G 6.2584-Cg, p.1/47190-pp 44 disease other 76 yes (44) unknown 4 H G 6.2584-Cg, p.1/471	×	p.culycoorap				polyps						
1 C M 6.284-K-G, p.1/yr179cy, e.1.187G-A, p.10/396ksp 46 alive 60-75 no no unknown unknown 3 C F 6.536k-K-G, p.1/yr179cys c.1.187G-A, p.10/396ksp 45 alive few 700 no unknown 4 C M 6.236k-K-G, p.1/yr179cys c.1.187G-A, p.10/396ksp 41 alive few no unknown 5 C M 6.236k-K-G, p.1/yr179cys c.1.187G-A, p.10/396ksp 44 disease other 76 yes (44) unknown 6 canner 76 yes (44) unknown 76 yes (44) (46) (46) (46) (46) (46) (46) (46)		36A>G; p.Tyr179Cys o	c.1187G>A; p.Gly396Asp	65		nmerous	yes (65)	00	unknown		nknown	
2 C M 6.2364-C6 pt/ydf290s c.1187C-Ac pt.03936ksp 41 alive few no no 4 C M 6.2364-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 41 alive few no no 5 C M 6.2364-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no than c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no than the c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no than the c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no than the c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no no c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no no c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no no c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no no c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no no c.236k-C6 pt/ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no no c.236k-C6 pt.ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no no c.236k-C6 pt.ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no c.236k-C6 pt.ydf290s c.1187C-Ac pt.04936ksp 44 alive few no no c.236k-C6 pt.ydf290s c.1187C-Ac pt.04936ksp 44 alive few no c.236k-C6 pt.04936ksp 44 alive few no c.236k-C6 pt.04836ksp 44 alive few no c.236ksp 44 alive fe	1 C M	36A>G; p.Tyr179Cys (c.1187G>A; p.Gly396Asp	46	alive	50-75	no	uo u	unknown		nknown	
3 C F c.536A-C; p.1yr179Oys c.1187G-A; p.6ly396Asp 45 alive 700 no 4 C M c.536A-C; p.1yr179Oys c.1187G-A; p.6ly396Asp 41 alive few no 5 c M c.536A-C; p.1yr179Oys c.1187G-A; p.6ly396Asp 44 disease other 76 yes (44) than c.536A-C; p.1yr179Oys c.1187G-A; p.6ly396Asp 44 disease other 76 yes (44) (46)	2 C M	36A>G: p.Tvr179Cvs	c.1187G>A; p.Glv396Asp			WE	no	unknown				
4 C M c.536k-Ci.p.Iyr/190s c.1187G-A.p.Gk/396ksp 41 aine few no c.536k-Ci.p.Iyr/190s c.1187G-A.p.Gk/396ksp 44 disease other 76 yes (44) than c.536k-Ci.p.Iyr/190s c.1187G-A.p.Gk/396ksp 44 disease other 76 yes (44) than c.536k-Ci.p.Iyr/190s c.1187G-A.p.Gk/396ksp 44 disease other 76 yes (44) (46)		364>G: p.Tvr179Cve	0.1187G>4: p.Glv396Acp	45			2	uwowluii				
4 C M C.536A-C; p.Iy179Oys C.1187G-A; p.Gly396Asp 41 allweer rew no C.536A-C; p.Iy179Oys C.1187G-A; p.Gly396Asp 44 disease other 76 yes (44) than c.536A-C; p.Iy179Oys C.1187G-A; p.Gly396Asp than cancer cancer (46)		SOAT BUILDING	C.T.C. C. C. C. C. C. C.	? :			2	I I				
5 C M c.536A>G; p.Tyn1790ys c.1187G>A; p.Gly396Asp 44 disease other 76 yes (44) r than cancer (45)	. A	36A>G; p. lyr179Cys	C.1187G>A; p.Gly396ASp	41			uo u	unknown				
than cancer cancer (46)	2 C	36A>G; p.Tyr179Cys (c.1187G>A; p.Gly396Asp	44	disease other	9/	yes (44)	unknown				
cancer (46)					than							
(46)					200000							
(46)					callcel							
					(46)							

	atient no.	Patient Index case no. (1)/relative	Index case (1)/relative Center Gender	3ender	Mutation 1	Mutation 2	Age" at diagnosis	Cause and age at death	Maximal polyp number colorectum	Colorectal C cancer (age ^a)	Sastroduodenoscopy (age*)	Gastroduodenoscopy No. and histology of Duodenal (age4) duodenal polyposis cancer	Duodenal	No. and type of gastric polyps	Extracolonic tumor (age at diagnosis)
1	l	e e	00	μΣ	c.536A>G; p.Tyr179Cys c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys c.1187G>A; p.Gly396Asp	45	alive	numerous 20–30	yes (45) no	yes (59) yes (62)	no no	2 2	none	cancer of soft
1 C M CATESTORY		Ħ	O	Σ	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	44	alive	>20	92	yes (45)	О	92	none	carcinoid tumor (62) sebaceous gland
C M C.536A-CR, D.M.1790ys C.1187G-A.R. D.B.938Aba 12 amount (1) 100 none		#	O	Σ	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp	36	alive	4	yes (37)	yes (38)	Ou	2	none	ancilollia (20)
March Ma		П	ပ	Σ	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	12	gastric	>100	OU.	yes (17)	no	00	none	gastric cancer (17)
C F CASSAD-Sig Dividuality CASSAD-Sig Dividuality Name Tribinal Name		2	O	Σ	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	14	(11)	>100	00	yes (14)	unknown		none	
This content (S) This conten			00	ωZ	c.536A>G; p.Tyr179Cys c.1438G>T; p.Glu480X	c.1187G>A; p.Gly396Asp c.1438G>T; p.Glu480X	20 00	CRC (60) disease other	multiple multiple	yes (58) yes (55)	yes (59) yes (55)	0 00		none	
C M C1187Ch-X. C.641G-D-A.D.G092GleSub G8 allwer multiple Per (3D) yes (43) non unknown unknown <t< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>than</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>								than							
0 H CL18767-A. CL1010464. 34 alwe multiple yes (35) yes (43) yes (44) no no 3 adenomas 0 F C.258A-C.G. DYM 1709c CL1870-A.R. Dolygedesy 43 alve unknown 149 yes (44) no no no no 3 adenomas 0 F C.258A-C.G. DYM 1709c CL1870-A.R. Dolygedesy alve unknown unknown no no no no no 0 F C.258A-C.G. DYM 1709c CL1870-A.R. Dolygedesy 34 alve unknown no no no no no 0 F C.258A-C.G. DYM 1709c CL1870-A.R. Dolygedesy 62 CRC (62) unknown yes no no no no no no no 0 F CL1870-A.R. Dolygedesy G CRC (62) unknown unknown unknown no no no no no 0 F CL18		1	ပ	Σ	c.1187G>A; p.Glv396Asp	c.647G>A; p.Gly216Glu	92	alive	22	yes (67)	по	unknown	unknown	unknown	
C F C.2586-C. P. INT/1790-S C.1188TO-A. L. Dol/Sedesay 43 althor Unknown Unknown <t< td=""><td></td><td>₽</td><td>ပ</td><td>Σ</td><td>c.1187G>A;</td><td>c.1101del,</td><td>36</td><td>alive</td><td>multiple</td><td>yes (36)</td><td>yes (43)</td><td>no</td><td></td><td>3 adenomas</td><td></td></t<>		₽	ပ	Σ	c.1187G>A;	c.1101del,	36	alive	multiple	yes (36)	yes (43)	no		3 adenomas	
C M CSSSRACE (p. PMYTPSQSe C. LISTRO-AV, Dok)-SSSRAS alie Unknown <		-	c	ш	c.536A>G: p.Tvr1 79Cvs	c.1187G>A: n.Glv396Asn	43	alive	61	ves (43)	ves (44)	00		none	
C F C.256A-CE, PLY179Ops C.1187G-A-K, Dol/9368Ap GRC Unknown unknown <t< td=""><td></td><td>2</td><td>O</td><td>Σ</td><td>c.536A>G; p.Tyr179Cys</td><td>c.1187G>A; p.Gly396Asp</td><td></td><td>alive</td><td></td><td>unknown</td><td>unknown</td><td></td><td></td><td></td><td></td></t<>		2	O	Σ	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp		alive		unknown	unknown				
C R C358AC-GR PAYTYSOS C1187G-A-X. poly39548-by CRC Unknown yes (57) windle poly39548-by CRC C1000-00-00-00-00-00-00-00-00-00-00-00-00		e	ပ	ш	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp		alive	unknown	unknown	unknown				
C F C1187G-A. C1187G-A. C1187G-A. C1187G-A. Dob/g3664sp GC CRC (GZ) Unknown yes (GZ) yes (GZ) no no <td></td> <td>4</td> <td>O</td> <td>Σ</td> <td>c.536A>G; p.Tyr179Cys</td> <td></td> <td></td> <td>CRC</td> <td></td> <td>yes</td> <td>unknown</td> <td></td> <td></td> <td></td> <td></td>		4	O	Σ	c.536A>G; p.Tyr179Cys			CRC		yes	unknown				
C F LTSTATIONAL LANGE AND AND MARKED AND AND MARKED AND AND AND AND AND AND AND AND AND AN		₩	O	ш	c.1187G>A;	c.1187G>A; p.Gly396Asp	22	alive	10	yes (57)	yes (64)	OU OU		none	lipoma
F		0	c	Σ	c.1187G>A:	c.11876>A: n.Glv3964sn	69		unknown	(62) vev	(62) vev	0		none	
C C.1187G-A; D40A3B6Asp 50 allee 1123 no unknown <			,		p.Gly396Asp	do constitution of the con	;	ì		(10)	(10)		<u>:</u>		
C F C1187G-A-K C1187G-A-K CRC unknown unknown<		H	O	ш	c.1187G>A; p.Glv396Asp	c.1187G>A; p.Gly396Asp	20	alive	123	00	ou	unknown	unknown	unknown	
C L187C-A: Doly/396Asp allhe unknown yes unknown C M 6.536A-G; DiVJ19Os £114770C 53 CRC (57) 11-30 yes (53) no unknown unknown C M £356A-G; DiVJ19Os £1047179Os £1047179Os </td <td></td> <td>7</td> <td>O</td> <td>ш</td> <td>c.1187G>A; p.Gly396Asp</td> <td>c.1187G>A; p.Gly396Asp</td> <td></td> <td>CRC</td> <td>unknown</td> <td>unknown</td> <td>unknown</td> <td></td> <td></td> <td></td> <td></td>		7	O	ш	c.1187G>A; p.Gly396Asp	c.1187G>A; p.Gly396Asp		CRC	unknown	unknown	unknown				
C M c.536A-CG, p.My179Os c.114776eC; 53 CRC (57) 11-30 yes (53) no unknown unk		ო	O	ш	c.1187G>A; p.Glv396Asp	c.1187G>A; p.Gly396Asp			unknown	yes	unknown				
C M C.356A-Ce p.Ny179Os C.356A-Ce p.Ny179Os G.30A-Ce p.Ny179Os G.30A-Ce p.Ny179Os C.356A-Ce p.Ny179Os		T	O	Σ	c.536A>G; p.Tyr179Cys	c.1147delC;	53	CRC (57)	11-30	yes (53)	ou	unknown	unknown	unknown	
C M C3580-06_p1N/1790s C3580-06_p1N/17790s C3580-06_p1N/17790s C35			c	2	6264 / G: n Turk 700 m	p.Ala385ProfsX25	C	(CS) amoudan	Cu	(20)	disconfun				
C M C.536A-C6, D.M.179Oys C.536A-C6, D.M.1779Oys C.536A-C6, D.M.179Oys		٠.	ی د	ΣΣ	c.330A > G. p. I yi I 790ys	c.5364>G: p.1y11/30ys	3 6	alive	50-100)es (20)	n common	Inknown	uwouduii	IIIIknown	
C M c.536k-Cg, p1yd1390s c.536k-Cg		-	0	Σ	c.536A>G; p.Tyr179Cys	c.536A>G; p.Tyr179Cys	30	alive	multiple	yes (30)	yes (30)	>10 adenomas	2	few; one	
C M c.358A-CG, p.ly/1790ys c.358A-CG, p.ly/1790ys 2.88 alive multiple no unknown		0	O	Σ	c.536A>G: p.Tvrt 79Cvs	c.5364>6: p.Tvr1790vs	58	alive	multiple	9	unknown			adenoma	
C M C.358A-C-G IN/17/1909s C.118TGD-A-M. Loky/308dsky 49 alies multiple no no no multiple no no multiple no no multiple no no multiple no no <td></td> <td>ı m</td> <td>O</td> <td>Σ</td> <td>c.536A>G; p.Tvr179Cvs</td> <td>c.536A>G; p.Tyr179Cvs</td> <td>78</td> <td>alive</td> <td>>100</td> <td>00</td> <td>unknown</td> <td></td> <td></td> <td></td> <td></td>		ı m	O	Σ	c.536A>G; p.Tvr179Cvs	c.536A>G; p.Tyr179Cvs	78	alive	>100	00	unknown				
C M c.358A-CE, p.Iyt/19Ops c.1817-A: p.loky39Asb alive unknown unknown unknown unknown C M c.358A-CE, p.Iyt/19Ops c.9334-3.42 30 alive 159 no		₩	O	Σ	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	49	alive	multiple	01	ou	unknown	unknown	unknown	
C M c.256A-Cg Pyly17909 10331-342		2	ပ	Σ	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp		alive	_	unknown	unknown				
C M c.358A-Cg. p1yr1390ps c.893 c.343-C C F c.558A-Cg. p1yr1390ps c.890 C3-x; p.61n230Gin 47 alive 200 yes (47) no unknown unknown none C F c.558A-Cg. p1yr1390ps c.1891C3-x; p.63p336Asp 53 alive 15 yes (53) no unknown unknown unknown sek C M c.538A-Cg. p1yr1390ps c.890 C3-x; p.63n230Gin 42 alive 120 no yes (43) no none se		Ħ	O	Σ	c.536A>G; p.Tyr179Cys	Trp131Arg	30	alive	152	DO OH	ou	unknown	unknown	unknown	
C F 6.586A-Cg.hy1790ys 6.080 G-Ay, p.Gln/230Gln 47 alive 200 yes (48) yes (50) no non none C F 6.558A-Cg.hy17190ys 6.080 G-Ay, p.Gln/230Gln 42 alive 120 no yes (43) no none se		H	O	Σ	c.536A>G; p.Tyr179Cys	c.933+3A>C	46	alive	119	yes (47)	ou	unknown	unknown	unknown	skin cancer (45)
C F c.536A-CG;p.Tyr179Cys c.1187G-X;p.Gby396Asp 53 alive 15 yes (53) no unknown unknown unknown unknown unknown c. M c.556A-CG;p.Tyr179Cys c.690 G-X;p.Gin230Gin 42 alive 120 no yes (43) no no no no se		₩	O	ш	c.536A>G; p.Tyr179Cys	c.690 G>A; p.Gln230Gln	47	alive	200	yes (48)	yes (50)	no		none	
C M c.558A>G; p.Ty179Cys c.690 G>A; p.din230Gin 42 allive 120 no yes (43) no none se		Η.	0	ш.	c.536A>G; p.Tyr179Cys	c.1187G>A; p.Gly396Asp	53	alive	15	yes (53)	ou	unknown		unknown	
		Н	ပ	Σ	c.536A>G; p.Tyr179Cys	c.690 G>A; p.Gln230Gln	42	alive	120	00	ves (43)	04	000	none	Sebaceous pland

ddine	upprementary rapid 1. (continued)													
Patient no.	astient Index case no. (1)/relative Center Gender	Center	Gender	Mutation 1	Mutation 2	Age" at diagnosis	Cause and age at death	Age" at Cause and Maximal polyp Colorectal allagnosis age, at death number colorectum cancer (age*)	Colorectal cancer (age*)	Cobrectal Gastrodachenoscopy No. and histology of Duodenal No. and type of Extracolomic tumor ancer (age*) (age*) duodenal polyposis carrier gastric polyps (age* at dagnosis	No. and histology of Duodenal N duodenal polyposis cancer a	Duodenal	No. and type of gastric polyps	Extracolonic tumor (age* at diagnosis)
20	1	O	ш.	c.536A>G; p.Tyrt.79Cys	c.536A>G; p.Tyr179Cys	31	alive	88	yes (57)	No.	unknown	unknown unknown	unknown	
z	=	o	ı	c,536A>G; p,Tyr179Cys c,536A>G; p,Tyr179C	c.536A>G; p.Tyr179Cys	33	alive	13	yes (60)	92	unknown	unknown unknown	unknown	
22	7	O	ı	c.536A>G; p.Tyrt.79Cys	lyr179Cys c.536A>G; p.Tyr179Cys	48	alive	multiple	yes (48)	yes (63)	no	2	o euoc	carcinoid tumor (49)
53	4	Ç	Σ	o.1147delC;	c.1147delC;	45	alive	>100	yes (45)	2	unknown	unknown	unknown	
				p.Ma385ProfsX25	p.Na385ProfsX25									
53	2	Ų	Σ	c.1147delC;	c.11.47 delC;	51	alive	30-40	yes (51)	u ou	unknown	unknown	unknown	
				p.Ala385ProfsX25	p.Ala385ProfsX25									
20	7	O	ı	c.11876>A;	Arg245His	48	alive	22	yes (41)	01	unknown	unknown	unknown	carcinoid tumor (42)
				p.GN396Asp										

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	М	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)	0.0000000
18	Breast	F	71	Infiltrating ductal carcinoma (grade II)	UK
561	Breast	F	60	Intracystic papillary carcinoma	German
-	510000		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.