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ARTICLE

Declining detection rates for *APC* and biallelic *MUTYH* variants in polyposis patients, implications for DNA testing policy

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Abstract

This study aimed to determine the prevalence of *APC*-associated familial adenomatous polyposis (FAP) and *MUTYH*-associated polyposis (MAP) in a large cohort, taking into account factors as adenoma count and year of diagnosis. All application forms used to send patients in for *APC* and *MUTYH* variant analysis between 1992 and 2017 were collected ($n = 2082$). Using the data provided on the application form, the *APC* and biallelic *MUTYH* prevalence was determined and possible predictive factors were examined using multivariate multinomial logistic regression analysis in SPSS. The prevalence of disease causing variants in the *APC* gene significantly increases with adenoma count while MAP shows a peak prevalence in individuals with 50–99 adenomas. Logistic regression analysis shows significant odds ratios for adenoma count, age at diagnosis, and, interestingly, a decline in the chance of finding a variant in either gene over time. Moreover, in 22% (43/200) of patients with FAP-related extracolonic manifestations a variant was identified. The overall detection rates are above 10% for patients with >10 adenomas aged <60 and >20 adenomas aged <70. Patients with variants outside these criteria had FAP-related extracolonic manifestations, colorectal cancer aged <40, somatic *KRAS* c.34G > T variant in the tumor or a first-degree relative with >10 adenomas. Therefore, *APC* and *MUTYH* testing in patients with >10 adenomas aged <60 and with >20 adenomas aged <70 is advised. Almost all FAP and MAP patients not meeting these criteria showed other characteristics that can be used as an indication to prompt genetic testing.

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Introduction

Due to a combination of environmental and low penetrant risk genetic factors [1–3], a large proportion of the general population will develop one or more adenomatous polyps (25% at age 50 and 50% at age 70 [4]). These polyps are possible precursors of colorectal carcinoma (CRC). The most commonly reported polyposis coli syndromes are *APC*-associated familial adenomatous polyposis (FAP) and *MUTYH*-associated polyposis (MAP) [5, 6]. Variants affecting the function of these genes are found in 8–10% of all patients with polyposis, depending on age and number of adenomas. Other forms of adenomatous polyposis explaining <1% of polyposis patients include *PolE/D*- [7], *NTHL1*- [8], *MSH3*- [9], *MBD4*- [10], and *MLH3*-associated polyposis [11]. Furthermore, mosaic *APC* variants are found in a substantial proportion of the remaining unexplained polyposis cases [12].

Identifying patients and family members with a genetic predisposition for polyposis is important due to the high

CRC risk that carriers face, even at a young age. This risk can be largely circumvented through regular surveillance and adenoma removal. Since adenomas after the age of 50 are common in the general population, offering genetic testing to all patients with adenomatous polyps is not yet cost effective. No clear guidelines for genetic testing existed until recently, and studies on the rates of variant detection have focused on patients with more than 20 adenomas lacking detailed information on the outcome of genetic testing in patients with less than 20 adenomas.

The present cohort consists of Dutch polyposis patients tested for *APC* and/or *MUTYH* variants between 1992 and 2017. The primary aim of this study was to determine the prevalence of *APC* and biallelic *MUTYH* disease causing variants in individuals referred to the clinical genetics department for DNA testing. Furthermore, we studied the relationship between the *APC* and *MUTYH* variants and several covariates. Based on these outcomes, guidelines were developed regarding the indications for referral to a clinical geneticist for DNA analyses.

Methods

Study population

This cross-sectional study was conducted amongst probands referred to a clinical geneticist (1992–2017) based on an individual's phenotype and/or family history of cancer and polyps. After consultation at centers across the Netherlands, blood samples and prespecified application forms were sent to the LUMC Laboratory of Diagnostic Genome Analysis (LDGA) for diagnostic analysis of the *APC* and *MUTYH* genes. The prespecified application form included age at testing, age at diagnosis of colorectal adenomas and/or CRC, personal history of other cancers, and a pedigree with relevant family information. The clinical information of the majority of the patients had been collected in databases developed for other studies [3, 13, 14]. These databases were merged and any required additional information was added. In total 2082 patients were included, exclusion criteria are listed in Fig. S1.

Although no clear guidelines existed, the presence of >10 adenomatous polyps was generally considered a reason for referral, as also advised by the American College of Gastroenterology (ACG) [15]. Moreover, FAP-related extracolonic manifestations were considered an indication for genetic *APC* testing and a somatic NM_033360.3 *(KRAS):* c.34G > T in tumor for *MUTYH* testing [16, 17].

Clinical genetic testing was performed with full gene Sanger sequencing and rearrangements were analyzed using multiplex ligation dependent probe amplification for the *APC* and *MUTYH* genes. *MUTYH* clinical diagnostics became available in 2004 [6], individuals suspicious for MAP but tested before 2004 were analyzed retrospectively.

Missing data

Due to incompletely filled in application forms, 26 patients were included with missing values for the age at first adenoma, 9 missed age at first CRC, and 164 patients missed family history. Possible explanations for a missing or incomplete pedigree information on the application form were adoption and no contact with family members.

Both the *APC* and *MUTYH* gene were sequenced in the majority of patients. However, in 387 (19%) and 339 (16%) patients only the *MUTYH* or the *APC* gene, respectively, was tested. The reasons for not testing these genes are summarized in Table S1.

Definitions

The terms "polyp" and "adenoma" were both used to describe patient samples sent for analysis. If no histology was mentioned, "polyps" were assumed to be adenomatous. After 2004, patients with hyperplastic/serrated polyps were occasionally sent for specifically *MUTYH* analysis [18]. Patients with exclusively serrated/hyperplastic type ($n = 19$) were treated separately in this study. Patients with other types of polyps such as hamartomatous or juvenile polyps were excluded.

Patients with a phenotype described as "FAP" ($n = 170$) or "polyposis" ($n = 19$) were considered to have >100 adenomas, "multiple adenomas/polyps" ($n = 206$) and "polyps" ($n = 14$) were categorized as 20–49 adenomas, and "some polyps" ($n = 11$) as less than 10 adenomas, as described previously [3]. Individuals without information on polyp history were excluded. Moreover, family members with 10 polyps or 'some' polyps were labeled as having <10 polyps, descriptions such as "FAP," "AFAP," and "multiple" were considered to have >10, and the bare description "polyps" as number unknown. When more than one first-degree relative (FDR) were reported with polyps, the highest number of polyps was used. Whenever multiple family members were diagnosed with CRC, the youngest was defined as the age of CRC in that family.

An *APC* de novo variant was assumed whenever the patients parents tested negative for the *APC* variant ($n = 10$) or whenever the pedigree showed no relevant cancers or polyps ($n = 69$).

Statistical methods

Multivariable logistic regression analysis was used to assess associations between variant status (yes/no) and covariates of interest. These covariates included cumulative polyp

count (<10, 10–19, 20–49, 50–99, and >100), age at diagnosis (<30, 30–39, 40–49, 50–59, and >60), history of CRC (no, <40, 40–50, and >50 (when multiple CRC, youngest age of diagnosis was used)), FDR with polys (no, yes <10, yes >10, and yes number unknown), with CRC (no, yes <50 years, yes >50 years, and yes age unknown), and year of analysis (<1995–1999, 2000–2005, 2006–2011, and 2012–2017). The patients without any adenomas were treated as a separate group.

Patients in whom *APC* or *MUTYH* was not tested were not included in the logistic regression analysis of the *APC* or *MUTYH* variant, respectively. All these patients were excluded from the analysis for overall variant detection.

Results were reported as odds ratios, with a 95% confidence interval, and a p-value < 0.05 was considered statistically significant. The statistical analyses were performed using SPSS statistics 23.

Results

Of the 2082 individuals included in the study (Table 1), in total, 14% ($n = 293$) carried an *APC* variant, 6% ($n = 119$) a biallelic *MUTYH* variant, and 2% ($n = 39$) a monoallelic *MUTYH* variant. Overall, a personal history of CRC was reported in 36% ($n = 746$) of patients. Notably, 16% ($n = 336$) had no history of adenomas whatsoever. In the overall cohort, variant detection rate is highest in patients with more than 20 adenomas (Fig. 1) and increases with younger ages (Fig. 2).

Association between phenotypic characteristics and a variant in *APC* and/or *MUTYH*

Multivariable logistic regression analysis (Table 2) shows that the odds of identifying a variant in either gene steadily increases with adenoma count. The odds of *APC* variant detection are highest in patients with >100 adenomas (OR 289.9; 95% CI 35.2–2385.2), while the odds ratio for biallelic *MUTYH* variants was highest for the 50–99 adenoma count (OR 10.8; 95% CI 4.0–29.1).

A personal history of CRC increased the likelihood of detecting biallelic *MUTYH* variants (<40: OR 3.9 [95% CI 1.5–10.0], 40–50: OR 4.5 [95% CI 2.2–9.0], and >50 OR

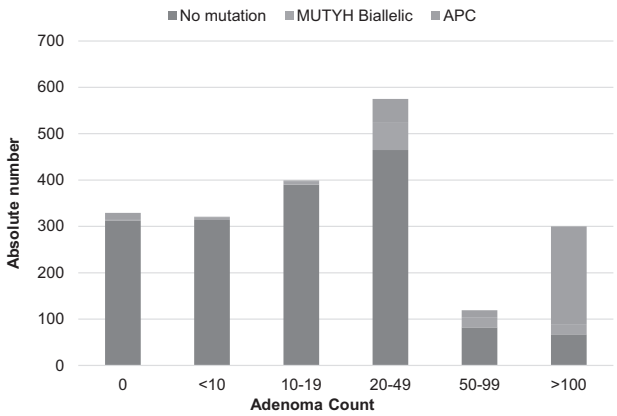

Fig. 1 Absolute numbers of patients sent in for genetic testing among the different adenoma count groups. *APC* and *MUTYH* variant detection depicted in green and yellow, respectively

Table 1 Cohort characteristics

	Total ($n = 2082$)	*APC*	Biallelic *MUTYH*	Monoallelic *MUTYH*
Male—*n* (%)	1202 (58%)	147 (50%)	64 (54%)	27 (69%)
Adenoma count				
0	336	13 (3.9%)	3 (0.9%)	7 (2.1%)
1–9	328	1 (0.3%)	6 (1.8%)	7 (2.1%)
10–19	406	3 (0.7%)	6 (1.5%)	7 (1.7%)
20–49	590	50 (8.5%)	60 (10%)	15 (2.5%)
50–99	122	15 (12%)	22 (18%)	3 (2.5%)
>100	300	211 (70%)	22 (7.3%)	0 (0%)
Mean age at adenoma diagnosis (min–max)	53 (4–84)	36 (9–68)	49 (21–75)	54 (23–77)
CRC, yes	746 (36%)	57 (7.6%)	82 (11%)	15 (2.0%)
Mean age at (first) CRC diagnosis (min–max)	53 (12–91)	41 (21–58)	49 (21–76)	57 (28–91)
FAP extracolonic manifestations, yes	200 (10%)	43 (22%)	8 (4.0%)	4 (2.0%)
FDR with polyps	728 (38%)	156 (21%)	46 (6.3%)	18 (2.5%)
Missing	164 (8%)	12 (7.3%)	4 (2.4%)	1 (0.6%)
FDR with CRC	811 (42%)	76 (9.7%)	42 (5.1%)	26 (3.2%)
Missing	164 (8%)	12 (7.3%)	4 (2.4%)	1 (0.6%)

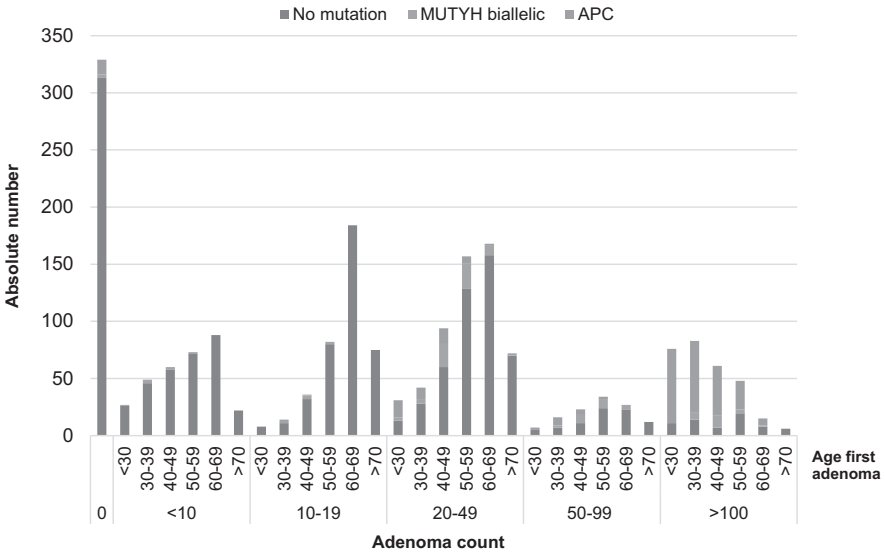

Fig. 2 Variant detection in different adenoma count groups, specified by age group

Table 2 Multivariate analysis

	APC or Biallelic *MUTYH*			*APC*			Biallelic *MUTYH*		
	N[a]	OR (95% CI)	*P*-value	*N*[a]	OR (95% CI)	*P*-value	*N*[a]	OR (95% CI)	*P*-value
Adenoma count									
<10	188	Ref	<0.001	205	Ref	<0.001	296	Ref	<0.001
10–19	292	2.6 (0.8–8.0)		296	8.5 (0.8–88.9)		367	1.5 (0.5–4.7)	
20–49	486	12.9 (5.0–33.3)		502	39.2 (4.7–324.2)		515	6.3 (2.6–15.1)	
50–99	114	15.5 (5.5–43.8)		115	32.5 (3.6–289.9)		116	10.8 (4.0–29.1)	
>100	264	59.4 (22.4–157.2)		275	289.9 (35.2–2385.2)		269	3.5 (1.3–9.5)	
Age at adenoma diagnosis									
>60	486	Ref	<0.001	502	Ref	<0.001	608	Ref	<0.001
50–59	328	5.1 (2.7–9.5)		335	3.3 (1.3–8.4)		370	3.9 (2.0–7.6)	
40–49	235	14.5 (6.8–31.0)		248	12.0 (4.6–31.4)		260	5.5 (2.3–13.5)	
30–39	164	11.4 (5.3–24.8)		172	12.6 (4.9–32.7)		188	3.9 (1.4–10.6)	
<30	131	18.7 (8.4–41.4)		136	33.1 (12.5–87.5)		137	0.9 (0.2–3.7)	
CRC (age)									
No	920	Ref	0.006	951	Ref	0.003	1065	Ref	<0.001
<40	56	1.3 (0.6–3.0)		58	0.6 (0.3–1.3)		63	3.9 (1.5–10.0)	
40–50	111	1.3 (0.7–2.5)		115	0.3 (0.1–0.6)		123	4.5 (2.2–9.0)	
>50	257	2.6 (1.5–4.5)		269	0.5 (0.2–1.1)		312	5.1 (2.8–9.2)	
FDR with polyps									
No	809	Ref	<0.001	834	Ref	<0.001	945	Ref	0.098
Yes, ≤10 polyps	140	0.5 (0.2–1.0)		153	1.5 (0.7–3.3)		191	0.3 (0.1–0.8)	
Yes, >10 polyps	184	4.5 (2.6–8.0)		191	4.5 (2.5–8.4)		194	1.2 (0.6–2.3)	
Yes, number unknown	211	0.4 (0.2–0.7)		215	0.4 (0.2–0.8)		233	0.8 (0.5–1.5)	
FDR with CRC									
No	812	Ref	0.007	842	Ref	0.155	923	Ref	0.193
Yes, ≤50 y	132	1.3 (0.7–2.4)		140	1.0 (0.5–2.1)		157	1.5 (0.8–2.9)	
Yes, >50 y	349	0.5 (0.3–0.8)		358	0.6 (0.3–1.0)		426	0.7 (0.4–1.3)	
Yes, age unknown	51	1.6 (0.6–4.3)		53	2.0 (0.7–6.0)		57	0.7 (0.2–2.3)	
Year of DNA testing									
2012–2017	401	Ref	<0.001	415	Ref	<0.001	511	Ref	0.006
2006–2011	511	1.7 (1.0–3.0)		521	2.0 (1.0–4.3)		591	1.1 (0.5–2.7)	
2000–2005	266	3.9 (2.2–7.2)		280	2.5 (1.2–5.4)		291	2.3 (1.2–4.7)	
<1995–1999	166	9.8 (4.7–20.3)		177	9.6 (4.1–22.2)		170	1.0 (0.5–2.0)	

[a]Numbers are without cases with missing information

5.1 [95% CI 2.8–9.2]). However, no effect was found for the detection of an *APC* variant.

The chance of finding a *MUTYH* or *APC* variant was not increased in patients with a FDR with CRC. Conversely, a FDR with >10 polyps did increase the odds of detecting an *APC* variant significantly (OR 4.5 [2.5–8.4]).

Variant detection rate trends over time

Also, the chance of finding a variant decreased over the last 20 years (<1995–1999: OR 9.8 [4.7–20.3], 2000–2005: OR 3.9 [2.2–7.2], and 2006–2011: OR 1.7 [1.0–3.0]). However, the odds of finding a biallelic *MUTYH* variant were highest between 2000 and 2005. Possibly explained by the introduction of *MUTYH* diagnostics in 2004, also attributing to the increase in number of patients sent in for DNA testing in general (Fig. 3).

APC and *MUTYH* detection rates in patients with less than 20 adenomas

Since a large number of patients with less than 20 adenomas underwent genetic testing ($n = 1070$, 51%), these categories are described in more detail.

No adenomas

The majority of patients without adenomas underwent testing due to CRC ($n = 176$), FAP-related extracolonic manifestations ($n = 75$), or both ($n = 11$). Nineteen had hyperplastic polyposis, while the rest were tested based on a positive family history. *APC* was tested in 203 and *MUTYH* was tested in 259 of these patients. Thirteen FAP and three MAP patients were detected in this group (Table S2). Nine of the *APC* variant carriers had extracolonic manifestations (mean age ~13, range 1.5–38). In addition, four had experienced CRC (two aged <40, one <50, and one >50). Of the MAP patients, all three had CRCs (<50 years old) with a *KRAS* c.34G > T transversion.

Of the 52 patients with solely CRC aged <40, 8% (2/24) had FAP and 4% (2/50) had MAP. In patients with CRC between age 40 and 50 years this was, respectively, 4% (1/24) and 2% (1/41).

1–9 adenomas

In patients with 1–9 adenomas ($n = 328$; *APC* tested $n = 217$ and *MUTYH* tested $n = 309$), one *APC* and six biallelic *MUTYH* variants were identified (2% variant detection rate). In this group the *APC* variant carrier already developed adenomas by the age of 20 and had a FDR with >100 polyps. Of the MAP patients, four were affected with CRC between the ages 39 and 53. Information on *KRAS* status in tumor DNA was available for one patient, showing a somatic *KRAS* c.34G > T transversion.

10–19 adenomas

Finally, in the group with 10–19 adenomas ($n = 406$; *APC* tested $n = 324$ and *MUTYH* tested $n = 401$) three FAP and six MAP patients were diagnosed who all developed adenomas aged under 60.

Aged above 70

No *MUTYH* or *APC* variants were found in patients with fewer than 20 adenomas aged above 70 years ($n = 82$). In the patients with more than 20 adenomas aged over 70 years, one MAP patient was found (1/90, 1.1%).

The prevalence of *APC* or biallelic *MUTYH* variants in different clinical phenotypes in patients with <20 adenomas is depicted in Table S3 (as adapted from Grover et al. [19]).

APC de novo

Based on family history, we surmise that a de novo variant has arisen in 24% of all *APC* variant carriers (69/292), which is comparable to the prevalence described previously [20]. This is also a plausible explanation for a negative family history in a number of FAP patients (Table S3).

Discussion

This study reports on 2082 individuals who underwent *APC* and *MUTYH* analysis at the LDGA between 1992 and 2017. The variant detection rates in patients with classic polyposis for FAP (70%) and MAP (7%) were comparable to previous studies [5, 21–24]. As expected, MAP showed a greater prevalence than FAP among individuals with 20–49 adenomas (FAP 9% vs. MAP 10%) and 50–99 adenomas (FAP 12% vs. MAP 18%). Notably, a recent study reported lower variant rates in all adenoma groups, possibly explained by the differences in clinical background (i.e., older age) and more recent years of diagnosis (2012–2016) [25].

Although most patients undergoing DNA analysis nowadays have fewer than 20 adenomas, clinical factors associated with the presence of a germline *APC* or biallelic *MUTYH* variants in this group are still poorly understood. A study by Grover et al. [19] reported a low variant detection rate, but no clinical description of the variant carriers was provided. The study from Stanich et al. [25] analyzed a large cohort of patients with 10–20 polyps, however no patients with less than ten polyps were included. In our cohort, a large group of individuals without adenomas ($n = 336$) was included.

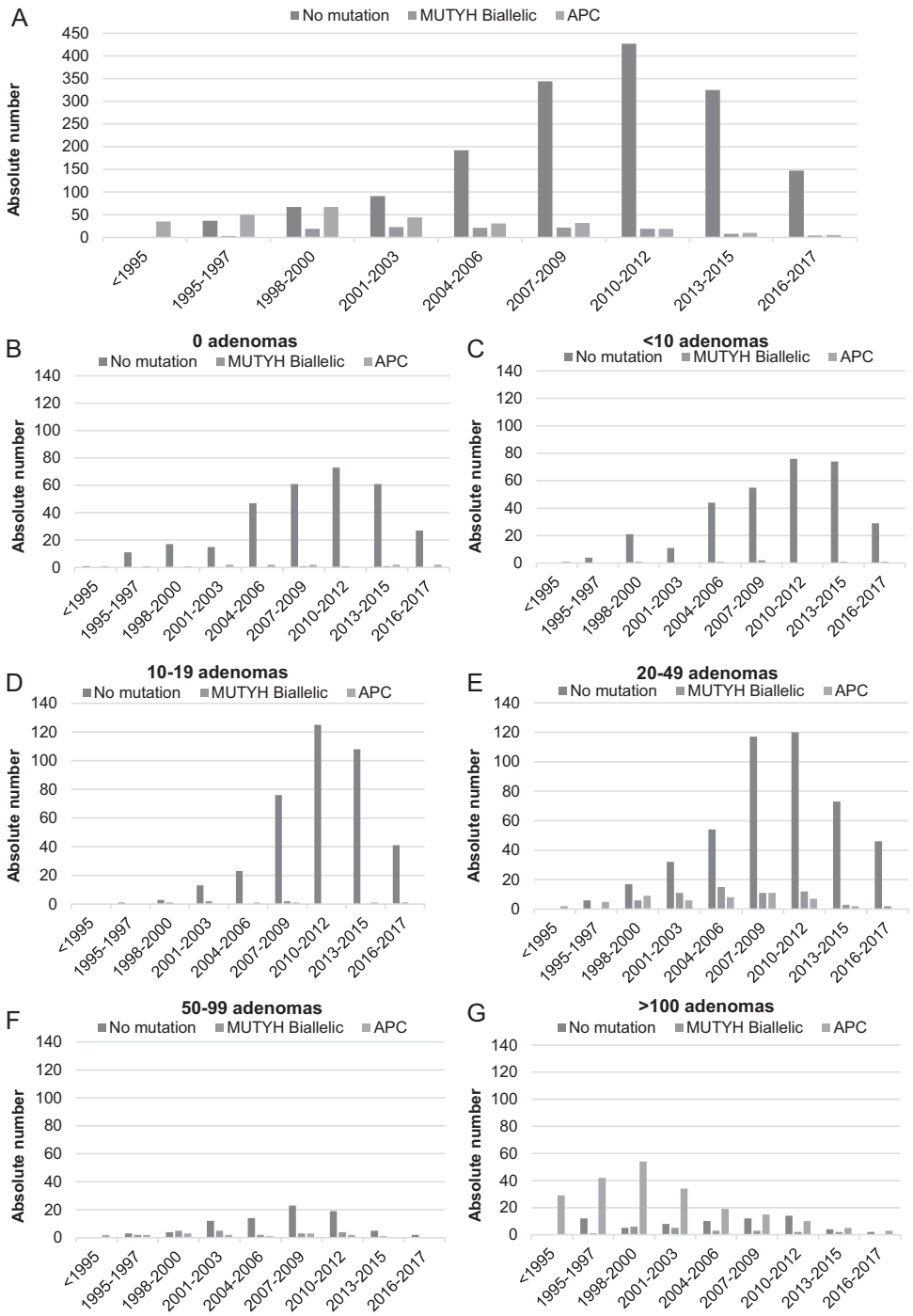

Fig. 3 Trends in variant detection. **a** *APC*/*MUTYH* variant detection in all adenoma groups. **b** Detection in patients without adenomas, **c** 1–9 adenomas, **d** 10–19 adenomas, **e** 20–49 adenomas, **f** 50–99 adenomas, and **g** more than 100 adenomas

Except for four MAP patients (Table S2), all patients with *APC* or biallelic *MUTYH* variants presented with >10 adenomas aged <60, >20 adenomas aged <70, CRC below age 40, a typical *KRAS* c.34G > T variant, a FDR relative with >10 polyps, or FAP-related extracolonic manifestations explaining their referral.

Since *KRAS* was not systematically analyzed in CRC cases, no variant detection rate could be determined for this cohort. Previous studies showed in 10–25% of the CRC cases with the *KRAS* c.34G > T variant a biallelic *MUTYH* variant. *KRAS* analysis in CRC is often performed because of the prognostic and therapeutic value [16, 17].

To analyze the impact on detection rates of several factors regression analysis was performed. While a younger age of first adenoma was associated with an increasing odds ratio of finding a variant in either gene, a personal history of CRC only increased the odds of finding a biallelic *MUTYH* variant, as also reported by Grover et al. [19]. This can

possibly be explained by the fact that known FAP patients undergo a (sub)total colectomy at an early age, effectively preventing the development of CRC. A family history of CRC did not influence the chance of finding either an *APC* or *MUTYH* variant. On the other hand, having a FDR with more than ten polyps clearly increased the chance of detecting an *APC* variant (OR 4.5, 2.5–8.4).

Increasing numbers of patients undergo DNA analysis while variant detection rate has steadily declined over the years. This resulted in an avoidable burden and expense for family cancer clinics and emphasizes the need for more stringent guidelines. One plausible explanation for the increase is the introduction of *MUTYH* gene testing in 2004, allowing milder phenotypes to be tested and thus increasing the number of patients with fewer than 20 adenomas. An alternative explanation is the introduction of population screening in the Netherlands in 2014 leading to increasing numbers of patients aged >55, with <10–20 adenomas. However, the total number of individuals declined after 2013, possibly due to other Dutch laboratories offering *MUTYH* and *APC* testing themselves. Finally, the introduction of more sensitive techniques, such as chromoendoscopy, improvement of endoscopy equipment, implementation of adenoma detection rate as a quality measure, and better bowel preparation, has led to improved adenoma detection, particularly of low stage and small adenomas (i.e., <0.5 mm) [26–28]. Moreover, a gradual incline in the percentage of de novo *APC* variants was seen over the years (<1995–1999: 14%, 2000–2005: 28%, 2006–2011: 36%, and 2012–2017: 29%), likely indicating that the majority of Dutch FAP families have been identified.

In 2015, the ACG issued guidelines for *APC* and *MUTYH* genetic testing in individuals with >10 cumulative colorectal adenomas, FAP-related extracolonic manifestations, or a family history of an adenomatous polyposis syndrome [15]. Based on our data, these guidelines may result in unnecessary testing, especially above the age of 60. On the other hand, Dutch guidelines also formulated in 2015 advise patients with either ten or more adenomas <60 years (cumulative) or 20 or more adenomas <70 years (cumulative) to be referred for genetic testing. The most recent NCCN guidelines [29] suggest genetic testing for all patients with >20 adenomas or a personal history of desmoid tumors, hepatoblastoma, cribriform-morular papillary thyroid cancer, and CHRPE, or patients with 10–20 adenomas with specific features such as age of onset influencing whether testing should be offered. Both these guidelines are supported by our data.

Stanich et al. [25] suggest testing in all patients with >10 polyps, regardless of histology or age despite their observation of declining variant rates with increasing age. Their reason is the observed detection rate in nonpolyposis related genes of around 5%. However, the 1% *CHEK2* variants reflects the prevalence in the general population [30] and does, in our opinion, not explain the polyposis phenotype. Furthermore, we excluded patients with MMR gene variants since further research is needed to draw firm conclusions about the association with polyposis.

CRC < 40 years in patients without adenomas might be a reason for testing, since variants were found in 9% and 4% of our cohort in, respectively, *APC* and *MUTYH*. Testing patients with adenomas above the age of 70 should on the other hand be undertaken with caution, since the variant detection rate was 1%. Of course, other more specific circumstances might warrant testing, such as polyps below age 20 and numerous primary CRC (≥2).

One weakness of this study was that not all patients with low adenoma counts were tested for both *APC* and *MUTYH*. We detected 4% *APC* and 1% biallelic *MUTYH* variants in 0 adenoma patients, <1% *APC* and 2% *MUTYH* in 1–9 adenoma patients, and 1% *APC* and 2% *MUTYH* in 10–19 adenomas patients. Based on the variant detection rate found in other studies, we anticipate that few or no cases were missed in our cohort [19, 31].

Moreover, variants in other genes were not taken into account. Many of the patients were tested for *PolE/D* [32], *MSH3*, and *NTHL1* on a research basis, the proven variant carriers were excluded in this study. Possible variants in other genes such as *SMAD4, BMPR1A*, and *PTEN* might be present, albeit in a small percentage of our cohort. In many labs, these genes have been included in NGS panels over the recent years, but, due to their rarity and often distinct phenotype, they do not justify lowering the suggested testing threshold. Nonetheless, in the near future the NGS panels will become more extensive, including more of other polyposis and colorectal cancer related genes as already proposed by the NCCN guidelines [29]. This will increase the yield of genetic testing also for other genes than *APC* and *MUTYH*.

The 2% heterozygote *MUTYH* carriers detected in this study is higher than expected based on the 1% prevalence reported in the Exome Aggregation Consortium database but similar to what Grover et al. [19] found in patients with <20 adenomas. It is possible that some monoallelic *MUTYH* carriers have other genetic factors, which combined with *MUTYH* explains adenoma development. As illustrated by two of the *APC* variant carriers also carrying a monoallelic *MUTYH* variant.

APC mosaicism was recently identified in 25–50% of unexplained patients with >20 adenomas [12]. In most of these cases, the mosaicism was undetectable in leukocyte-derived DNA and required testing of DNA isolated from >2 adenomas. Tumor testing is still logistically challenging and not performed in the current cohort. However, it might be an efficient approach in the future, especially for low adenoma count patients.

Conclusion

Adenoma count, age at adenoma diagnosis, and year of analysis are important predictive factors for *APC* and *MUTYH* variants. In view of the decline in variant detection, careful consideration for gene testing, especially in patients with lower polyp counts, is advised. Nevertheless, *APC* and *MUTYH* testing seems indicated in patients with >10 adenomas aged <60 and >20 adenomas aged <70. Other indications for referral are FAP-related extracolonic manifestations, CRC aged <40, a somatic *KRAS* c.34G > T transversion, or a FDR with >10 adenomas.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics The study was approved by local ethics review boards (P01.019).

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