HHS Public Access

Author manuscript

Fam Cancer. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

Fam Cancer. 2021 April ; 20(2): 111–116. doi:10.1007/s10689-020-00198-x.

CHARACTERIZING GERMLINE *APC* AND *MUTYH* VARIANTS IN ASHKENAZI JEWS COMPARED TO OTHER INDIVIDUALS

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Abstract

Background: Germline variants in the *APC* and *MUTYH* genes contribute to colorectal cancer (CRC) and adenoma risk, though may occur with varying frequencies in individuals of different ancestries. The aim of this study was to evaluate the prevalence of *APC*, monoallelic *MUTYH* and biallelic *MUTYH* germline variants in Ashkenazi Jewish (AJ) and Other Ancestry (OA) individuals with colorectal adenomas.

Methods: We studied 7,225 individuals with colorectal adenomas who had germline *APC* and *MUTYH* testing at a commercial laboratory. Cross-sectional medical history data were extracted from provider-completed test requisition forms. We performed bivariate analysis to compare the frequency of *APC* and *MUTYH* variants between AJ and OA, and examined *APC* p.I1307K and monoallelic *MUTYH* carrier phenotypes using logistic regression.

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DECLARATIONS

Disclosures: Dr. Syngal is a consultant for Myriad Genetics and Digital China Health Technologies, and has rights to an inventor portion of the licensing revenue from PREMM$_5$. The authors report no other conflicts of interest.

Availability of data and material: Data sharing is not applicable to this manuscript as we analyzed an existing and previously reported dataset in this study.

Code availability: Not applicable

Results: Pathogenic *APC* variants occurred in 38/285 AJ (13%) and 1342/6940 OA (19%; *P*=0.09); biallelic *MUTYH* variants in 2/285 (1%) AJ and 399/6940 (6%) OA (*P*<0.0001); *APC* p.I1307K in 35/285 (12%) AJ and 29/6940 (1%) OA (*P*<0.0001); and monoallelic *MUTYH* in 2/285 (1%) AJ and 133/6940 (2%) OA (*P*=0.06). Monoallelic *MUTYH* variants were significantly associated with having a personal history of CRC, regardless of ancestry (OR 1.78; 95% CI 1.21–2.49; *P*<0.01), but no significant association was found between *APC* p.I1307K variants and personal history of CRC (OR 1.38; 95% CI 0.79–2.44; *P*=0.26).

Conclusion: Ashkenazim with colorectal adenomas rarely have monoallelic or biallelic *MUTYH* variants, suggesting different genetic etiologies for polyposis in AJ compared to OA individuals. AJ ancestry assessment may be important in clinical evaluation for polyposis.

Keywords

Founder mutation testing strategy; *MUTYH*-associated polyposis; ancestry; polyposis in Ashkenazim

INTRODUCTION

Colorectal adenomas are known precursors to colorectal cancer (CRC) and occur frequently in individuals with inherited polyposis syndromes including Familial Adenomatous Polyposis (FAP), Attenuated Familial Adenomatous Polyposis (AFAP), and *MUTYH*-associated polyposis (MAP). Inherited adenomatous polyposis syndromes account for 1% of all colorectal cancers and are currently characterized by elevated cumulative adenoma counts and the presence of germline pathogenic variants in the *APC* (FAP and AFAP), *MUTYH* (MAP), *GREM1, MSH3, POLE, POLD1* or *NTHL1* genes [1, 2]. Individuals affected by hereditary adenomatous polyposis syndromes have an elevated lifetime risk of CRC which often necessitates specialized clinical management including risk-reducing total colectomy, and/or regular endoscopic surveillance, as well as extracolonic surveillance. Genetic evaluation is also recommended for first and second-degree relatives of the index mutation carrier to identify at-risk relatives [1].

Genetic evaluation of suspected polyposis includes germline analysis of the *APC* and *MUTYH* genes which has led to the frequent identification of moderate-risk gene variants such as *APC* p.I1307K- a common *APC* variant in Ashkenazim, and monoallelic *MUTYH* variants - seen in 1 in 50 Caucasians [3]. Both *APC* p.I1307K and monoallelic *MUTYH* variants have been associated with moderately increased risk for CRC but not polyposis, and their frequency in unique populations suggests that ancestry may also play a key role in their underlying prevalence [1, 4, 5].

Understanding the contributions of these moderate risk variants and ancestry to hereditary polyposis can inform clinical practice and facilitate early detection and cancer prevention in at-risk populations. The aim of this study was to examine the contributions of germline *APC* and *MUTYH* variants (including the *APC* p.I1307K variant and monoallelic *MUTYH* variants) to polyposis and CRC risk in Ashkenazi Jews (AJ) versus to Other Ancestry individuals (OA) from a large cohort of individuals referred for clinical germline evaluation

of suspected inherited polyposis. This study builds on previous work and is focused on the Ashkenazi Jewish subgroup [6].

MATERIALS AND METHODS

Study Population

The study cohort consisted of 8,676 unique individuals with a personal or family history of colorectal cancer or colorectal adenomas that underwent germline genetic testing for the *APC* and *MUTYH* genes at a commercial laboratory (Myriad Genetics, Inc.) between 2004 and 2011, as part of standard clinical care, as previously described [7].

Ordering clinicians completed a pre-specified test order form that included the individuals' age at testing, ancestry (Western/Northern European, Central/East European, Ashkenazi, Latin American/Caribbean, African, Asian, Near East/Middle Eastern, Native American, other), cancer history (CRC, other), age at cancer diagnosis, age at colorectal adenoma diagnosis, cumulative adenoma count and family history of cancer (cancer type and age at diagnosis). We excluded individuals with no reported personal history of colorectal adenomas. Individuals were characterized as Ashkenazi Jewish (AJ) if their clinicians selected "Ashkenazi" ancestry on the test requisition form, including individuals for whom multiple ancestries were indicated. All others, including those for whom ancestry information was missing, were classified as Other Ancestry (OA) individuals.

Germline Analysis

All study subjects underwent full sequencing and large rearrangement analysis of the *APC* gene, and gene analysis of the two most common *MUTYH* variants in Western/Northern Europeans- c.536A>G (p.Y179C) and c.1187G>A (p.G396D), or full sequencing of the *MUTYH* gene. For individuals whose initial *MUTYH* testing included only the two common European founder variants, reflex full *MUTYH* sequencing was performed if either the p.Y179C or p.G396D variant was detected, as previously described [7]. Deleterious or 'suspected' deleterious germline variants were classified as pathogenic while all others were categorized as non-pathogenic [7]. For this analysis, the *APC* p.I1307K variant was not considered pathogenic and was analyzed separately from other *APC* variants. Likewise, individuals with monoallelic pathogenic *MUTYH* variants were counted separately from those with biallelic pathogenic *MUTYH* variants.

Statistical Methods

The primary outcome was the presence of pathogenic germline *APC* variants, biallelic *MUTYH* variants, *APC* p.I1307K variant and monoallelic *MUTYH* variant, stratified by AJ and OA ancestry. Covariates of interest were the cumulative number of colorectal adenomas, age at first colorectal adenoma, age at genetic testing, personal history of CRC, and CRC in a first-degree relative. Colorectal adenoma count variables (1–19, 20–99 and ≥100 adenomas) and age at genetic testing (<30, 30–39, 40–49, 50–59, and ≥60 years) were analyzed as ordinal variables.

Bivariate analysis was used to assess the association between ancestry and covariates of interest. Fisher exact tests were performed for binary variables or categorical variables with expected frequencies <5. Otherwise, we performed chi-square tests for categorical variables, and t-tests for continuous variables. A two-sided p-value of <0.05 was considered statistically significant. Logistic regression with Fisher exact tests was used to compare the frequencies of pathogenic *APC, APC* p.I1307K, biallelic *MUTYH*, or monoallelic *MUTYH* variants, between AJ and OA individuals stratified by adenoma count, while controlling for age at genetic testing.

As previously described, coefficients from five rounds of multiple imputation performed in R (Areg Impute function) were combined to obtain final estimates for missing data such as colorectal adenoma count, age at colorectal adenoma diagnosis and age at CRC diagnosis [7]. Multivariable logistic regression on this imputed dataset was used to examine the association between personal history of CRC and the moderate risk alleles (*APC* p.I1307K and monoallelic *MUTYH* variants), controlling for colorectal adenoma count, ancestry, first-degree relative with CRC, and age at genetic testing. Statistical analyses were performed using SAS (version 9.4, SAS institute Inc.), and R (version 3.4.1, R Foundation for Statistical Computer).

RESULTS

We excluded 1,451 individuals with no personal history of colorectal adenomas resulting in a final study population of 7225 subjects, of whom 3566 (49%) were male. The average age at the time of genetic testing and at first colorectal adenoma diagnosis were 52.5 years (SD ±15.4), and 45.0 years (SD±15.0) respectively. Twenty-two percent (1567/7225) of the cohort had ≥ 100 cumulative adenomas, 47% (3420/7225) had 20–99 adenomas, and 31% (2238/7225) had 1–19 adenomas (Table 1). Twenty-five percent (1779/7225) of subjects had a personal history of CRC and 30% (2235/7225) had a family history of CRC in one or more first-degree relatives.

All subjects underwent complete *APC* analysis and at least targeted *MUTYH* testing for the common *MUTYH* European variants, and 16% (1147/7225) of the overall cohort underwent complete *MUTYH* sequencing. There was no significant difference in the proportion of AJs (19%, 53/285) and OAs (16%, 1094/6940; P=0.21) that underwent complete analysis of the *MUTYH* gene. AJ individuals in this study were on average older (55 years vs. 52 years; P<0.01) than OAs at the time of genetic testing. Colorectal adenoma distribution differed between AJ and OA in the 1–19 adenoma (40% AJ, 115/285 and 31% OA, 2123/6940) and ≥100 colorectal adenoma groups (14% AJ, 39/285 and 22% OA, 1528/6940; P<0.001). There was no significant difference in gender distribution, age at first colorectal adenoma diagnosis, personal/family history of colorectal cancer (CRC) or genetic test offerings, in AJ compared to OA (Table 1).

There was no significant difference in pathogenic *APC* variants between AJ (13%, 38/285) and OA (19%, 1342/6940; P=0.09). The *APC* p.I1307K variant was predominantly found in AJ (12%, 35/285) and was comparably rare in OA (1%, 29/6940; P <0.0001). Biallelic *MUTYH* variants were less common in AJ (1%, 2/285) than OA (6%, 399/6940; P

<0.0001), as were monoallelic *MUTYH* variants (1% AJ, 2/285 and 2% OA, 133/6940; $P = 0.06$). Almost all biallelic and monoallelic *MUTYH* carriers were OA (99%, 532/536) (Table 1).

For both AJ and OA individuals, the combined prevalence of pathogenic *APC* and biallelic *MUTYH* variants was highest among individuals with ≥100 cumulative adenomas. There was no significant difference in the proportions of AJ and OA with pathogenic *APC* or biallelic *MUTYH* variants by adenoma count, except among individuals with 20–99 cumulative adenomas, where biallelic *MUTYH* pathogenic variants were significantly lower among AJ individuals (1/131, 1%) compared to OA individuals (243/3289, 7%; $P<0.01$) (Table 2).

The *APC* p.I1307K variant was significantly more common among AJ individuals with 1–19 adenomas (OR 27.43; 95% CI 12.48–61.53) and 20–99 adenomas (OR 34.61; 95% CI 14.87–82.69) versus OA individuals but, was rarely seen in either AJ and OA individuals with ≥ 100 adenomas (0 AJ vs. 0.1% OA (2/1528); $P=1$) (Table 2). Although monoallelic *MUTYH* variants were rarely seen in AJ individuals, there was no significant difference in the prevalence of monoallelic *MUTYH* variants in AJ versus OA individuals when stratified by adenoma count.

Using multivariable regression to adjust for adenoma count, ancestry, family history of CRC, and age at genetic testing, there was no significant association between *APC* p.I1307K and a personal history of CRC (OR 1.38; 95% CI 0.79–2.44; $P=0.26$), although carrying monoallelic *MUTYH* variants was significantly associated with a personal history of CRC (OR 1.78; 95% CI 1.21–2.49; $P<0.01$).

DISCUSSION

In this large, cross-sectional study of a consecutive cohort of individuals referred for germline genetic testing for polyposis, we found significantly different genetic contributors to polyposis in AJ individuals compared to OA individuals. In particular, biallelic pathogenic germline *MUTYH* variants were reasonably common in OA individuals with both attenuated and classic type polyposis, but were rarely seen in AJ, suggesting that *MUTYH* variants play a minimal role in inherited polyposis for AJ individuals. Furthermore, we observed a significant albeit modest association between personal history of CRC and the presence of a monoallelic germline *MUTYH* variant, suggesting that such variants may indeed confer mildly elevated risk of CRC even in the absence of a polyposis phenotype.

Ashkenazim are known to have a higher population prevalence of certain germline variants that predispose to various forms of cancer. Ashkenazi Jewish founder variants occur in a variety of genes including *APC*, *BRCA1*, *BRCA2, CHEK2*, *GREM1*, *MSH2*, and *MSH6*, which collectively increase risks for colorectal, gastric, pancreatic, breast, ovarian, and other cancers [8]. Understanding the prevalence of pathogenic variants by ancestry can inform the delivery of personalized cancer risk assessment in distinct populations. For instance, since 1 in 40 Ashkenazim carries a *BRCA1* or *BRCA2* pathogenic variant, guidelines from the

United States Preventive Services Task Force now endorse routine germline testing for these founder variants for all Ashkenazim, regardless of personal/family cancer history [9].

Prior to the advent of Next-Generation Sequencing technology, germline analysis for hereditary polyposis was limited to single gene analysis of the *APC* and *MUTYH* genes via Sanger sequencing. *APC* gene analysis comprised of full gene sequencing while *MUTYH* gene analysis often started with only targeted sequencing for the two European founder *MUTYH* variants - p.Y179C or p.G396D, followed by full *MUTYH* gene sequencing if one of the founder variants was identified [7]. In a retrospective review of 1,522 individuals that underwent full *MUTYH* sequencing after *MUTYH* gene analysis for p.Y179C or p.G396D, 56% (48) of 85 biallelic *MUTYH* carriers reported Western/Northern European ancestry and none reported Ashkenazi descent, indicative of low prevalence of *MUTYH* variants among Ashkenazim [10]. In another study of 189 consecutive CRC cases reporting Ashkenazi ancestry, founder variant testing failed to identify the p.Y179C or p.G396D variants [11]. Despite similar *MUTYH* testing offerings across our study, we identified few Ashkenazi individuals with monoallelic and biallelic *MUTYH* variants in keeping with both reports of the rarity of *MUTYH* variants in Ashkenazim, and the limited utility of targeted *MUTYH* testing in non-Western European populations. Our study highlights that testing for the p.Y179C or p.G396D *MUTYH* variants is very low yield in AJ individuals even among those with an MAP oligopolyposis phenotype, either because *MUTYH* plays a minor role in Ashkenazim polyposis or because AJ individuals require full *MUTYH* sequencing to identify those with *MUTYH*-associated CRC risk. Our study may have been underpowered to detect a significant difference in the 1–19 and ≥100 colorectal adenoma groups.

Moderate risk gene variants such as *APC* p.I1307K and monoallelic *MUTYH* are common incidental findings on multigene panel testing for CRC susceptibility and also on panels for other indications [2, 12, 13]. Technological advancements in gene analysis have decreased the price of germline genetic testing by as much as 67%, thus allowing the provision of multigene genetic testing which analyzes a wide range of genes in parallel, compared to step-wise testing for syndrome-specific genes which we now know has clear limitations [2, 14]. Our results add to the existing literature by depicting the commonality of *APC* p.I1307K (present in 12% of Ashkenazim in our study) and monoallelic *MUTYH* (in 2% of Other Ancestry individuals) variants in specific populations and the implications for polyposis risk assessment in clinical practice. In addition, the growing availability and utilization of multigene testing through non-traditional means such as direct-to-consumer testing services, suggests the increased identification of *APC* p.I1307K and monoallelic *MUTYH* carriers who would benefit from regular colonoscopic surveillance for cancer prevention.

Our findings of a modest association between monoallelic *MUTYH* carriage and CRC risk support the results from prior studies which found monoallelic *MUTYH* carriers had a 2 to 2.5-fold increase in CRC risk, suggesting that there may be benefit to some degree of increased colonoscopic surveillance in monoallelic *MUTYH* carriers [5, 15]. Similarly, a 2013 study that examined the clinical importance of screening for *APC* p.I1307K in 3,305 consecutive Israeli patients undergoing colonoscopic surveillance found a 1.75-fold elevated risk for CRC in Ashkenazi Jewish *APC* p.I1307K carriers, compared to non-carriers [16].

Although we did not find a significant association between *APC* p.I1307K carriage and CRC, our study may have been underpowered to detect this association since <1% of our study cohort carried the *APC* p.I1307K variant unlike the higher 8% carrier rate in the surveillance study [15].

The strengths of this study include our ability to analyze a large group of consecutive individuals referred for *APC* and *MUTYH* gene testing with detailed personal and family history, which provides a representative snapshot of clinical test cohorts. Our findings therefore highlight how to utilize syndrome-specific testing where multigene panel genetic testing is unaffordable or unavailable. However, we recognize the limitations of our study including the use of a high-risk cohort of individuals specifically referred for evaluation of suspected inherited polyposis, and the relatively small number of Ashkenazim in the cohort. Furthermore, ancestry and polyp count were ascertained from clinician report, and we were unable to verify the accuracy and completeness of such data. We were also unable to discern the specific indications for genetic testing referral or the geographic distribution of the study population. Our cohort predated the availability of multigene panel genetic testing, and thus we do not have data on other forms of inherited polyposis (e.g. germline *GREM1* variants, which have been reported almost exclusively in Ashkenazim) that could be underlying the patients' polyposis. With that said, these findings do have important implications in the multigene panel testing era, since monoallelic *MUTYH* variants and *APC* p.I1307K variants are among the most common incidental findings on such testing, given their high population prevalence.

In spite of these limitations, the findings from this study highlight the rarity of Ashkenazi Jewish *MUTYH* carriers and underscores the need for at least, complete *MUTYH* gene analysis in individuals of Ashkenazi ancestry. Complete analysis of the *MUTYH* gene is especially relevant in practices and health systems that are yet to adopt multigene testing since targeted *MUTYH* testing would be sub-optimal and result in the missed detection of some monoallelic *MUTYH* carriers. Furthermore, requesting an inappropriate, syndrome-specific genetic test may preclude subsequent access to the appropriate genetic test option and thereby undermine prompt identification of clinically-actionable germline findings.

Genetic testing remains the gold standard for diagnosing inherited cancer syndromes and will likely continue to expand beyond genetics specialties in order to intensify the early identification and management of at-risk populations. Individuals can now access genetic testing through direct-to-consumer companies and ancestry ascertainment platforms such as 23andMe, which now offers testing for the p.Y179C or p.G396D *MUTYH* European founder variants in its genetic testing package [17]. As cancer risk assessment and genetic testing becomes the standard of care, clinicians would benefit from guidance on approaches to genetic evaluation including considerations for ancestry, as well as the interpretation of common incidental findings.

In summary, our findings demonstrate the differing contributions to inherited polyposis among AJ versus OA individuals and strongly suggest that limiting *MUTYH* analysis to founder variant testing is of particularly low yield. Genetic testing in Ashkenazi individuals with polyposis should include complete analysis of the *APC* and *MUTYH* genes, especially

in resource-limited settings without access to multigene panel testing. Presently, marketed colorectal multigene panels include the newer polyposis genes such as *GREM1*, *NTHL1*, *MSH3*, *POLE* and *POLD1.* More studies are required to evaluate the contributions of *MUTYH* and these newer genes to polyposis in ethnic populations, to leverage the increasing availability of genetic testing and to inform clinical practice.

Acknowledgments

Funding support: Supported by the National Institutes of Health 2R01CA132829 (Dr. Syngal), The Pussycat Foundation *Helen Gurley Brown Presidential Initiative* (Dr. Ukaegbu) and the National Institutes of Health T32 GM007748 (Dr. Ukaegbu)

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Table 1.

Description of the study population

	Total n = 7225 (%)	Ashkenazi n = 285 (%)	Other Ancestry n = 6940 (%)
Male	3566 (49)	156 (55)	3410 (49)
Age at genetic testing, Mean ± SD	52.5 ± 15.4	55.4 ± 16.2	52.4 ± 15.3
Age at first colorectal adenoma diagnosis, Mean ± SD	45.0 ± 15.0	45.8 ± 15.8	44.9 ± 14.9
Colorectal adenoma count, No.			
≥100	1567 (22)	39 (14)	1528 (22)
20–99	3420 (47)	131 (46)	3289 (47)
1–19	2238 (31)	115 (40)	2123 (31)
Personal history of colorectal cancer	1779 (25)	64 (23)	1715 (25)
First-degree relative with colorectal cancer	2235 (30)	81 (28)	2154 (31)
Genetic test offerings			
Complete *APC* gene analysis	7225 (100)	285 (100)	6490 (100)
Targeted *MUTYH* gene analysis (for p.Y165C and p.G382D)	7225 (100)	285 (100)	6490 (100)
Complete *MUTYH* gene analysis	1147 (16)	53 (19)	1094 (16)
Genetic testing results			
Pathogenic *APC*	1380 (19)	38 (13)	1342 (19)
Biallelic *MUTYH*	401 (6)	2 (1)	399 (6)
Monoallelic *MUTYH*	135 (2)	2 (1)	133 (2)
APC p.I1307K	64 (1)	35 (12)	29 (1)
No *APC* or *MUTYH* variants	5245 (73)	5037 (73)	208 (73)

45 individuals (5 Ashkenazi and 40 Other Ancestry) with missing age at genetic testing

Table 2.

Genetic testing results, by colorectal adenoma count and ancestry

Colorectal adenoma count, No.	Ashkenazi n (%)	Other Ancestry	Odds Ratio (95% CI)*	*P* value
		n (%)		
1–19	115 (100)	2123 (100)		
Pathogenic *APC*	3 (3)	99 (5)	0.57 (0.11–1.80)	0.50
Biallelic *MUTYH*	0 (0)	58 (3)	0.23 (0–1.02)	0.11
Monoallelic *MUTYH*	1 (0.9)	39 (2)	0.47 (0.01–2.81)	0.76
APC p.I1307K	19 (17)	14 (0.7)	27.43 (12.48–61.53)	*<0.0001*
No *APC* or *MUTYH* variants	74 (64)	1752 (83)	0.38 (0.25–0.58)	*<0.001*
20–99	131 (100)	3289 (100)		
Pathogenic *APC*	14 (11)	339 (10)	1.30 (0.65–2.43)	0.48
Biallelic *MUTYH*	1 (1)	243 (7)	0.11 (0.003–0.61)	*<0.01*
Monoallelic *MUTYH*	1 (0.8)	77 (2)	0.23 (0- ∞)	0.11
APC p.I1307K	16 (12)	13 (0.4)	34.61 (14.87 – 82.69)	*<0.0001*
No *APC* or *MUTYH* variants	82 (63)	2369 (72)	0.57 (0.39 – 0.85)	*<0.01*
≥100	39 (100)	1528 (100)		
Pathogenic *APC*	21 (54)	904 (59)	1.03 (0.49 – 2.21)	1.00
Biallelic *MUTYH*	1 (3)	98 (6)	0.31 (0.008 – 1.93)	0.38
Monoallelic *MUTYH*	0	17 (1)	1.50 (0 – 7.13)	1
APC p.I1307K	0	2 (0.1)	12.78 (0 – 108.54)	1
No *APC* or *MUTYH* variants	15 (38)	438 (29)	1.31 (061 – 2.73)	0.54

*Adjusting for age at genetic testing