HHS Public Access

Author manuscript

Genet Med. Author manuscript; available in PMC 2016 June 13.

Published in final edited form as:

Genet Med. 2015 October ; 17(10): 815–821. doi:10.1038/gim.2014.199.

Racial variations in frequency and phenotypes of APC and *MUTYH* mutations in 6,169 individuals undergoing genetic testing

Jennifer A. Inra, MD[1,2], **Ewout W. Steyerberg, PhD**[3], **Shilpa Grover, MD, MPH**[1,2], **Ashley McFarland, MPH**[4], **Sapna Syngal, MD, MPH**[1,2,5], and **Fay Kastrinos, MD, MPH**[4,6]

[1]Division of Gastroenterology, Brigham and Women's Hospital, Boston, MA [2]Harvard Medical School, Boston, MA [3]Center for Medical Decision Making, Erasmus Medical Center, Rotterdam, the Netherlands [4]Division of Digestive and Liver Diseases, Columbia University Medical Center, New York, NY [5]Population Sciences Division, Dana-Farber Cancer Institute, Boston, MA [6]Herbert Irving Comprehensive Cancer Center, New York, NY

Abstract

Purpose—To assess whether differences in frequency and phenotype of *APC* and *MUTYH* mutations exist among racially/ethnically diverse populations.

Methods—6169 individuals with personal and/or family history of colorectal cancer (CRC) and polyps were studied. *APC* testing involved full sequencing/large rearrangement analysis (FS/LRA); *MUTYH* involved "panel testing" (for Y165C, G382D mutations), or FS/LRA, performed by Myriad Genetics, a commercial laboratory. Subjects were identified as Caucasian, Asian, African American (AA), or Other. Statistical tests included Chi-Square, Fisher's Exact, ANOVA and *z*-approximation.

Corresponding Author: Fay Kastrinos, MD, MPH, 161 Fort Washington Avenue, Suite 862, New York, NY 10032, Tel: 212-342-5643; Fax: 212-305-5576, fk18@columbia.edu.

Conflict of Interest: none

CONTRIBUTIONS

Jennifer A. Inra: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, approval of manuscript for submission

Ashley McFarland: analysis and interpretation of data, critical revision of the manuscript for important intellectual content, statistical analysis, approval of manuscript for submission.

Ewout W. Steyerberg: analysis and interpretation of data, critical revision of the manuscript for important intellectual content, approval of manuscript for submission

Shilpa Grover: analysis and interpretation of data, critical revision of the manuscript for important intellectual content, approval of manuscript for submission

Sapna Syngal: study concept and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, obtained funding, administrative, technical or material support, study supervision, approval of manuscript for submission

Fay Kastrinos: study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, obtained funding, administrative, technical or material support, study supervision, approval of manuscript for submission

Supplementary information is available at the *Genetics in Medicine* website.

Results—17.5% had pathogenic *APC* mutations. 4.8% were biallelic *MUTYH* carriers. 18% were non-Caucasian with >100 adenomas and younger ages of adenoma or CRC diagnosis ($p<0.0001$) than Caucasians. The overall *APC* mutation rate was higher in Asians, AAs and Others compared to Caucasians (25.2%, 30.9%, 24%, 15.5%;$p<0.0001$) but similar in all groups when adjusted for polyp burden. More *MUTYH* biallelic carriers were Caucasian or Other than Asian or AA (5%, 7%, 2.7%, 0.3%;$p<0.0001$). Among Caucasians, 5% were biallelic carriers identified by panel testing versus 2% by sequencing/LRA ($p=0.002$). Among non-Caucasians, 3% undergoing panel testing were biallelic carriers versus 10% identified by sequencing/LRA($p<0.0002$).

Conclusion—Non-Caucasians undergo genetic testing at more advanced stages of polyposis and/or younger ages of CRC/polyp diagnosis. Restricted *MUTYH* analysis may miss significant numbers of biallelic carriers, particularly in non-Caucasians.

Keywords

Familial Adenomatous Polyposis (FAP); *MUTYH* Associated Polyposis (MAP); genetic testing; phenotype; race

INTRODUCTION

Approximately 5% of colorectal cancers (CRC) diagnosed annually are attributed to highly penetrant genetic syndromes. Of these, familial adenomatous polyposis (FAP), an autosomal dominant condition, is associated with the development of hundreds to thousands of adenomas in carriers of germline mutations in the adenomatous polyposis coli (*APC*) gene. Carriers of the classically defined syndrome have a near 100% lifetime risk of developing CRC in the absence of medical or surgical intervention since colorectal adenomas often develop in the second decade and require intensive endoscopic evaluation. Up to 10% of *APC* gene mutation carriers have a milder presentation referred to as “attenuated” FAP (AFAP), with fewer than 100 colorectal adenomas that, along with CRC, can manifest at older ages.

However, an *APC* gene mutation may not be detected in up to 20% of patients with a classic FAP phenotype and up to 90% with an attenuated polyposis phenotype (1). Another form of polyposis cause by alterations in the *MUTYH* gene, leads to an entity known as *MUTYH*-associated polyposis (MAP). MAP is an autosomal recessive syndrome most often associated with an attenuated polyposis phenotype and is caused predominantly by two commonly detected missense mutations, Y165C and G382D (2). Patients with AFAP and MAP may have similar clinical features and the conditions may be indistinguishable. Both have an increased risk of CRC with few polyps and present at older ages, as compared to the easily recognizable classic polyposis phenotype of FAP (1, 3–5).

The majority of information regarding the genetic epidemiology, phenotypic characteristics, and cancer risks and preventive strategies related to FAP and MAP has been reported from studies involving mostly Caucasian individuals from North America, Western Europe and/or Australia (6–10). However, data from non-Caucasian individuals of diverse ancestral backgrounds has been limited. The goals of this study were to evaluate and compare the presence of *APC* and *MUTYH* mutations and associated phenotypic characteristics among

different ethnic and racial groups in a large cohort of subjects in the United States who had undergone genetic testing for these genes through Myriad Genetics Laboratory, a large US commercial laboratory. In addition, we assessed the proportion of gene variants detected in *APC* and *MUTYH* and the frequency of *MUTYH* mutations beyond the known common gene hotspots.

MATERIALS AND METHODS

Study Population

Data for this cross-sectional study was obtained from 8676 individuals who underwent genetic testing for both the *APC* and *MUTYH* mutations between 2004 and 2011 (1). Patients were selected for genetic testing by health care providers due to their personal and/or family history of colorectal polyps and/or CRC. Clinically relevant information related to each subjects' cancer and polyp history, along with family cancer history, were obtained from a test requisition form completed by the provider and submitted along with the patients' blood samples to Myriad Genetics Laboratory. Information included age at testing, personal cancer history, age at cancer diagnosis, adenoma count (options pre-specified as 0, 1, 2–5, 6–9, 10–19, 20–99, 100–999 and ≥1000), family history of CRC and polyps (including degree of relation, cancer site, age at diagnoses). Data on ancestry was obtained from the following pre-specified categories: Western/Northern European, Central/Eastern European, Ashkenazi, Latin American/Caribbean, African, Asian, Near/Middle Eastern, Native American, or Other ancestry. Only those subjects who reported one ancestry were included. Patients that did not report any ancestry, reported multiple ancestries or had incomplete polyp and/or CRC information were excluded.

Individuals were classified into the following four race/ethnicity groups: (1) Caucasian (Western/Northern European, Central/Eastern European, Ashkenazi ancestry), (2) Asian, (3) African American, and (4) Other (Latin American/Caribbean, Near/Middle Eastern, Native American, Other). The latter category was comprised of combined groups due to the small sample size in each individual group. We defined these groups as "race/ethnicity" because the information was self-reported and subjects may have responded based on a biological or social context. "Ancestry" and "race" are biological identifications with a particular group, which do not necessarily relate to cultural or environmental characteristics, while "ethnicity" can relate to cultural identification among individuals who may or may not have a common genetic origin. Therefore, the use of "race/ethnicity" incorporates both a biological and cultural interpretation.

The study was investigator-initiated. Data collection and statistical analysis occurred independently. The collection of clinical data and molecular analyses occurred at Myriad Genetic Laboratories Inc. An anonymized dataset was provided to the Dana-Farber Cancer Institute/Columbia University Medical Center investigators for all data analyses, which was conducted by clinical researchers (JI, FK) who are not affiliated with Myriad Genetic Laboratories Inc. The study was approved by the institutional review boards at Dana-Farber Cancer Institute and Columbia University Medical Center.

Laboratory Methods

As previously described (1), all subjects had undergone *APC* and *MUTYH* gene testing. Subjects had full gene sequencing and large rearrangement analysis of the *APC* gene. Full gene sequence determination was performed in the forward and reverse direction of approximately 8532 base pairs comprising 15 exons and 420 adjacent noncoding intronic base pairs. For large rearrangement analyses, all exons of the *APC* were examined for evidence of deletions and duplications by standard Southern blot methods.

All individuals also underwent DNA sequence analysis of *MUTYH*, but the mutational analyses performed varied among subjects. The type of *MUTYH* testing conducted was based on the providers' specification on the test requisition form. Options included (1) sequencing specific portions of *MUTYHHH* designated to detect the two most common mutations (Y165C and G382D), also referred to as "panel testing," or (2) full *MUTYH* gene sequencing without initial restriction of DNA mutational analysis to the two most common mutations. When one of the common gene mutations was detected on "panel testing", full gene sequencing was conducted reflexively, without need for a specific request by the provider.

Directed DNA sequence analysis was performed on exons 7 and 13, which are designed to detect the mutations Y165C and G382D. Full sequence analysis was performed in both the forward and reverse directions of approximately 1608 base pairs comprising 16 exons and approximately 450 adjacent non-coding intronic base pairs. The non-coding intronic regions of *MUTYH* that were analyzed do not extend more than 20 base pairs proximal to the 5' end and 10 base pairs distal to the 3' end of each exon. Aliquots of patient DNA were each subjected to polymerase chain reaction (PCR) amplification reactions. The amplified products were each directly sequenced in forward and reverse directions using fluorescent dye-labeled sequencing primers.

Individuals with deleterious or suspected deleterious mutations in either the *APC* or *MUTYH* gene were defined as having pathogenic mutations. We only report on results of biallelic *MUTYH* mutation carriers. The presence of recurrent pathogenic mutations among non-Caucasians was evaluated for both genes and when identified, the presence in Caucasians (whether in this dataset and/or reported in published literature or public databases) was also assessed. Individuals with suspected polymorphisms were defined as having nonpathogenic mutations. Individuals with gene mutations whose association with FAP and MAP disease risk is unknown were defined as having variants of unknown significance (VUS). DNA mutational analyses techniques did not change during the study period.

Statistical Methods

The primary outcome of interest was the frequency of pathogenic *APC* and *MUTYH* mutations among the four race/ethnicity groups. Secondary outcomes of interest were to compare genotype-phenotype characteristics among gene mutation carriers in the four race/ethnicity groups by assessing adenoma count, age at adenoma diagnosis, personal history of CRC, age at CRC diagnosis, and history of CRC in a first-degree relative. For subjects with

adenomas identified more than once, a cumulative adenoma count was computed. Adenoma count was a categorical variable (0, <10, 10–19, 20–99, 100–999, ≥1000 adenomas). In subjects diagnosed with CRC more than once, the age at diagnosis was defined as the age at first diagnosis. Age was analyzed as a continuous variable. All categorical and binary variables were analyzed by a Chi-square Test or Fisher's Exact Test and reported as proportions with 95% confidence intervals. All continuous variables were analyzed by analysis of variance and were reported as mean values with standard errors and 95% confidence intervals. The z approximation test compared differences between two proportions. A two-sided *p*- value of <0.05 was considered statistically significant.

For missing data related to adenoma counts and age at adenoma diagnosis, a multiple imputation approach was used as previously reported to obtain estimates (1). The coefficients of five rounds of imputation (performed in R using the ArgeImpute function) were combined to obtain the final estimates for missing data. All other statistical analyses were performed using SAS version 9.2 (SAS Institute Inc).

RESULTS

Subject Characteristics

Data from 8676 individuals who had undergone genetic testing for both the *APC* and *MUTYH* genes was analyzed. Subjects who did not report any race or ethnicity or provided more than one race or ethnicity were excluded. 6169 subjects were included; Table 1 provides data on the participants' characteristics. The majority of subjects (5041/6169, 81.7%) were Caucasian and 151 (2.5%) were Asian, 382 (6.2%) were African American and 595 (9.6%) were of Other race/ethnicity. Among all subjects, 5176 (83.9%) reported a personal history of adenomas with a mean age of 45 years at the time of first diagnosis. A personal history of CRC was reported in 1660/6169 (27%) individuals and the mean age at diagnosis was 46.5 years. The majority of subjects with CRC also reported having adenomas (1292/1660, 21%) while only 6% of all subjects had CRC but no adenomas. The majority of patients with adenomas had <100 polyps (4074/5236). Lastly, 1929/6169 (31.3%) of the subjects reported a first-degree relative with CRC.

Presence of *APC* Gene Mutations and Phenotypic Characteristics of Mutation Carriers

Over seventeen percent of subjects (1081/6169, 17.5%) were identified as *APC* mutation carriers (Table 2). Among Caucasians, 782/5041 (15.5%) had a pathogenic *APC* mutation detected. The *APC* mutation rate in the Asian, African and Other groups was almost twice the rate as compared to Caucasians (25.2%, 30.9%, 24% respectively; p<0.0001). Among all *APC* mutations carriers, there were no significant differences in the phenotypic characteristics between any of the race/ethnicity groups, including number of adenomas, age at adenoma diagnosis, presence and age of CRC, and first-degree relates with CRC (Table S1, Table S2). Non-Caucasians more often reported a personal history of both CRC and adenomas than Caucasians (p=0.05). There was no difference in the frequency of pathogenic *APC* mutations according to polyp counts between Caucasians and non-Caucasians. There were no recurrent pathogenic *APC* mutations identified among non-Caucasians that were associated with a particular phenotype. The majority of recurrent mutations identified among

non-Caucasian carriers were also seen in Caucasians. Table S5 includes data on recurrent *APC* gene mutations among non-Caucasian carriers and associated phenotypes.

Six percent of all subjects undergoing *APC* testing (399/6169) were found to have a VUS (Table 2). The highest proportion of VUS was detected among Asians and African Americans. Eleven percent of Asians and African Americans had a VUS (17/151, 43/382 respectively) versus 6% for Caucasians and Other (303/5041, 36/595 respectively; p<0.0001) (Table 2). The *APC* I1307K alteration was more prevalent among Caucasians (55/303, 18.5%) versus Other (3/36, 8.3%). None were detected among African Americans or Asians.

Presence of *MUTYH* Gene Mutations and Phenotypic Characteristics of Mutation Carriers

Nearly five percent (298/6169, 4.8%) of subjects were identified as biallelic *MUTYH* mutation carriers and most were Caucasian (250/298, 84%) (Table 2). The prevalence of biallelic *MUTYH* mutations among all Caucasian subjects was 5% (250/5041) compared to 2.7% in Asians (95% CI, 0.7–6.6), 0.3% in African Americans (95% CI, 0.01–1.5) and 7.2% in Others (95% CI, 5.3–9.6) (Table S1). There were no significant phenotypic differences among the biallelic *MUTYH* mutation carriers when stratified by race/ethnicity (Table S3, Table S4). The majority of *MUTYH* gene mutation carriers had an attenuated polyposis phenotype with <100 polyps (225/298, 75%), regardless of race/ethnicity. There was no difference in the frequency of biallelic *MUTYH* mutations according to polyp count between Caucasians and non-Caucasians. Upon review of the mutation spectrum associated with pathogenic *MUTYH* gene mutations, the E466X mutation, was solely identified among Asian individuals. All other recurrent mutations identified among non-Caucasians were also reported in Caucasians.

Of all subjects who underwent genetic testing for *MUTYH*, 0.9% (55/6169) were found to have a VUS (Table 2). The highest VUS rates were in Asians (3/151, 2%) and African Americans (12/382, 3.1%) as compared to Caucasians (39/5041, 0.8%) and Others (1/595, 0.2%,); (p<0.0001).

DNA Mutational Analysis for the Identification of Biallelic *MUTYH* Mutation Carriers

Eighty-nine percent (5491/6169) of all subjects undergoing DNA mutational analysis for *MUTYH* had “panel testing” for Y165C and G382D, while 11% (678/6169) had full sequencing/large rearrangement analysis. Of all Caucasians who were identified as biallelic *MUTYH* mutation carriers, 5% (239/4526) were identified by “panel testing,” while only 2% (11/515) were identified using full sequencing/large rearrangement analysis (p=0.002) (Table 3). Of all non-Caucasians who were identified as biallelic *MUTYH* mutation carriers, only 3% (31/965) were identified by “panel testing,” while 10% (17/163) were identified using full sequencing/large rearrangement analysis (p<0.0002). Table S6 provides data on recurrent *MUTYH* gene mutations among non-Caucasian carriers and associated phenotypes.

Clinical Characteristics of All Subjects Undergoing Genetic Testing Stratified by Race or Ethnicity

As there were no differences in phenotypic characteristics of *APC* and biallelic *MUTYH* gene mutation carriers among the four racial/ethnic groups despite variation in the frequency of deleterious mutations, we assessed the eligible subjects' clinical characteristics at time of genetic testing. An attenuated polyposis phenotype was more prevalent among Caucasians than non-Caucasians (≤10, 11–19, 20–99; p=0.15, 0.02 and 0.06 respectively; Table 4). Conversely, all non-Caucasian groups had a higher prevalence of the classic polyposis phenotype compared to Caucasians, with more individuals reporting 100–999 adenomas and ≥1000 adenomas (p<0.0001 and p=0.009 respectively). The mean age at adenoma diagnosis for non-Caucasians was younger than that of Caucasians (43.4 vs 45.4 years). Specifically, Asians, African Americans and Others had mean ages of 43.5 years [95% CI, 41.2–45.7], 43.9 years [95% CI, 42.5–45.2] and 42.9 years [95% CI, 41.8–44.1] respectively, while Caucasians had a mean age of 45.4 years [95% CI, 45–45.76] (p<0.0001).

There were no differences regarding personal history of CRC with or without history of adenomas (p=0.11, 0.39 respectively) and presence of a first-degree relative with CRC (p=0.07) between the four racial/ethnic groups (Table 5). However, similar to age of adenoma diagnosis, the mean age at CRC diagnosis was younger in non-Caucasians than in Caucasians (43.7 vs. 47.3 years), where Asians, African Americans and Others were diagnosed at mean ages of 44.8 years [95% CI, 40.7–48.6], 44.6 years [95% CI, 42.0–47.3] and 41.7 years [95% CI, 39.4–44.0] respectively (p<0.0001).

DISCUSSION

This study is the largest to examine the results of genetic testing for *APC* and *MUTYH* gene mutations among individuals from diverse ethnic and racial backgrounds with history of CRC and adenomas. Our initial objective was to determine whether there were differences in disease manifestations among mutation carriers of different ethnic groups, which have not been studied extensively thus far. We found no differences in phenotypic characteristics among *APC* and biallelic *MUTYH* mutation carriers who were Caucasian, Asian, African American, or of Other race or ethnicity, but surprisingly, there were significant differences in the frequency of *APC* and *MUTYH* gene mutations among these groups. These differences are most likely due to selection of patients undergoing genetic testing, or methods of DNA mutational analyses used, rather than inherent biologic differences between the groups. Overall, non-Caucasian patients more often had a history of colorectal adenomas and/or CRC diagnosed at younger ages and a stronger polyposis phenotype compared to Caucasians, who were older at the time of adenoma/CRC diagnosis and had an attenuated polyposis phenotype. As the majority of non-Caucasian subjects undergoing testing had a more severe presentation than Caucasians, it is not surprising that the *APC* mutation rate in the Asian, African American and Other patient groups was significantly higher.

Conversely, among individuals with biallelic *MUTYH* gene mutations, the mutation frequency was significantly higher among Caucasians and Others compared to Asians and African Americans. These results may be attributed to the variable approaches of DNA mutation analyses in the detection of *MUTYH* gene mutations. In this study, 89% of all

subjects tested for *MUTYH* alterations had analyses limited to the common Y165C and G382D mutations, while only 11% of subjects had full sequencing/large rearrangement analysis. The current practice for detecting *MUTYH* gene mutations begins with analysis of either Y165C or G382D mutations (11) and among Caucasians, these missense mutations account for the majority of pathogenic *MUTYH* mutations detected, where up to 93% of biallelic mutation carriers carry at least one of these two “hotspots” (12). However, other mutations may be more frequent in non-Caucasians and potentially missed by restricted mutational analysis. For example, the E466X mutation has been commonly reported in Pakistani or Indian individuals with MAP (13) and was also a recurrent mutation among the Asian biallelic *MUTYH* carriers in our study. While a limited testing strategy may miss deleterious mutations in all patients undergoing *MUTYH* genetic testing, the impact may be particularly pronounced among non-Caucasians. Among the non-Caucasian biallelic MUTYH gene mutation carriers, 17/48 (35%) would not have been identified if testing had been limited to detection of the two common missense mutations.

In contrast to MAP, FAP has been more extensively studied and multiple studies have reported on the prevalence of *APC* gene mutations and genotype-phenotype correlations among carriers related to disease severity, age of polyp and cancer onset and the presence of extracolonic manifestations (14–16). However, these data have been derived predominantly from Caucasian subjects enrolled in North American, Australian, or European familial cancer registries. While some studies suggest that the prevalence of certain *APC* gene mutations may vary worldwide (17–19) and that some ethnic variation in the clinical presentation of FAP may exist (20), results have been inconsistent and limited by the small patient populations assessed. The results of our study do not support there being any phenotypic differences between *APC* gene mutation carriers of different races and ethnicities. We also did not identify any specific recurrent mutations among non-Caucasians to be associated with a particular phenotype.

Highly penetrant polyposis syndromes are easily recognized and are likely to prompt genetic evaluation. A more subtle presentation, as associated with attenuated polyposis, may be less recognized and the opportunity to refer patients for genetic evaluation may be missed. Individuals with ten or more cumulative adenomas should be considered for genetic evaluation and testing for germline *APC* or *MUTYH* mutations (21) as supported by recent evidence that increasing number of adenomas, as well as young age of adenoma onset, are strong predictors of carrying a deleterious *APC* or *MUTYH* gene mutation (1). However, studies report that physicians that predominantly care for non-Caucasian patients are less likely to order genetic testing or recommend genetic evaluation and counseling (22). Although our study cannot address why non-Caucasian patients with polyposis less often undergo genetic testing, we speculate that a number of issues may exist beyond the healthcare providers’ lack of referral. Patients may not appreciate the benefits of genetic testing for attenuated polyposis, as the burden of disease among family members may be less apparent and perception of inherited CRC risk and acceptance of genetic testing may be different between different ethnic/racial groups. Studies have shown that African Americans and Hispanics are less knowledgeable about genetic testing for certain diseases compared to Caucasians, and African Americans are less confident in the benefits of genetic testing (23–25). There may also be significant differences in insurance coverage of genetic testing for

individuals with an attenuated polyposis phenotype which may have a more substantial negative impact on individuals of lower socioeconomic status and/or underrepresented racial/ethnic backgrounds (26). These issues were beyond the scope of our study and may be areas for future research.

Our study has a number of important strengths. It represents a nationwide sample of patients diagnosed with CRC and/or adenomas undergoing genetic testing and is the largest cohort of *APC* and *MUTYH* mutation carriers studied to date. It includes a diverse population from different ethnic and racial backgrounds and allows us to explore the impact of variable genetic testing approaches in different populations, particularly for the detection of *MUTYH* alterations. We were able to examine differences in the spectrum of *APC* and *MUTYH* mutations in different racial/ethnic groups, particularly the frequency of VUS. We found a higher detection rate of VUS for both genes among non-Caucasians. The rate of VUS detected in the *APC* gene was near double among Asians and African American compared to Caucasians and individuals of Other race or ethnicity. While the overall frequency of VUS was much lower in the *MUTYH* gene (0.9%), the pattern was similar to *APC* VUS among the different groups. While the current methods used to classify VUS are complex, studies that include racially and ethnically diverse populations are necessary.

There are also a number of potential limitations related to this study. Misclassification of race and ethnicity may have been possible as this information was gathered by self-report and subjects were required to answer in pre-defined categories. In an attempt to minimize misclassification, eligibility was limited to only those subjects who reported one race/ethnicity. A more updated race and ethnicity classification system, such as the one currently supported by the FDA for use in clinical trials (which combines both race and ethnicity in each predefined category), would have been preferred and should be considered for future studies. In addition, the data was provided by a single, commercial laboratory and relies on clinical information reported on the mandatory test requisition form where verification of diagnoses and collection of additional data was not possible. Although reporting errors may occur, the fact that health care professionals are the sources of data likely minimize those based on incorrect diagnoses, and results using similar datasets have been validated using external data from familial cancer registries (27, 28). Lastly, the overall prevalence of biallelic *MUTYH* gene mutation carriers is low, even more so for non-Caucasian patients, despite the large number of patients undergoing testing for CRC and polyposis. This may limit our interpretation of results pertaining to genotype-phenotype correlations among non-Caucasian individuals with *MUTYH* gene mutations.

In summary, the results of this study provide new insight on the current practices and patterns of predictive testing for *APC* and *MUTHY* mutations among a large, racially and ethnically diverse population undergoing genetic testing in the US for colorectal adenomas and CRC. High detection rates of *APC* mutations among non-Caucasians of Asian and African descent likely relate to testing patients with a severe clinical presentation of classic polyposis and young onset of CRC than individuals with an attenuated polyposis phenotype. Conversely, fewer *MUTYH* gene mutations were detected among non-Caucasians and likely relates to the decreased uptake of full gene sequencing for *MUTYH* where selective DNA mutational analysis may miss pathogenic *MUTYH* mutations among these patients.

Additional studies that examine the contribution of race/ethnicity on the genetic epidemiology related to inherited CRC syndromes are needed, as are studies on the possible barriers related to genetic testing for cancer susceptibility among diverse patient populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank Lynn Ann Burbidge, BS and Richard J. Wenstrup, MD of Myriad Genetics Laboratories Inc for their assistance in data retrieval and preparation.

Financial support: NIH/NCI K07 CA151769 (Fay Kastrinos), NIH/NCI K24113433 (Sapna Syngal)

REFERENCES

1. Grover S, Kastrinos F, Steyerberg EW, et al. Prevalence and phenotypes of *APC* and *MUTYH* mutations in patients with multiple colorectal adenomas. JAMA. 2012; 308(5):485–492. [PubMed: 22851115]
2. Sampson JR, Jones N. MUTYH-associated polyposis. Best Pract Res Clin Gastroenterol. 2009; 23(2):209–218. [PubMed: 19414147]
3. Russell AM, Zhang J, Luz J, et al. Prevalence of *MUTYH* germline mutations in Swiss *APC* mutation-negative polyposis patients. Int J Cancer. 2006; 118(8):1937–1940. [PubMed: 16287072]
4. Renkonen ET, Nieminen P, Abdel-Rahman WM, et al. Adenomatous polyposis families that screen *APC* mutation-negative by conventional methods are genetically heterogeneous. J Clin Oncol. 2005; 23(24):5651–5659. [PubMed: 16110024]
5. Jenkins MA, Croitoru ME, Monga N, et al. Risk of colorectal cancer in monoallelic and biallelic carriers of *MUTYH* mutations: A population-based case-family study. Cancer Epidemiol Biomarkers Prev. 2006; 15(2):312–314. [PubMed: 16492921]
6. Aceto G, Curia MC, Veschi S, et al. Mutations of *APC* and *MUTYH* in unrelated Italian patients with adenomatous polyposis coli. Hum Mutat. 2005; 26(4):394. [PubMed: 16134147]
7. Enholm S, Hienonen T, Suomalainen A, et al. Proportion and phenotype of *MUTYH*-associated colorectal neoplasia in a population-based series of Finnish colorectal cancer patients. Am J Pathol. 2003; 163(3):827–832. [PubMed: 12937124]
8. Gismondi V, Meta M, Bonelli L, et al. Prevalence of the Y165C, G382D and 1395delGGA germline mutations of the MYH gene in Italian patients with adenomatous polyposis coli and colorectal adenomas. Int J Cancer. 2004; 109(5):680–684. [PubMed: 14999774]
9. Isidro G, Laranjeira F, Pires A, et al. Germline MUTYH mutations in Portuguese individuals with multiple colorectal adenomas. Hum Mutat. 2004; 24(4):353–354. [PubMed: 15366000]
10. Vandrovcova J, Stekrova J, Kebrdlova V, et al. Molecular analysis of the *APC* and *MUTYH* genes in Czech families affected by FAP or multiple adenomas: 13 novel mutations. Hum Mutat. 2004; 23(4):397. [PubMed: 15024739]
11. Goodenberger M, Lindor NM. Lynch Syndrome and *MYH*-Associated Polyposis: Review and Testing Strategy. J Clin Gastroenterol. 2011; 45:488–500. [PubMed: 21325953]
12. Sampson JR, Dolwani S, Jones S, et al. Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of *MUTYH*. Lancet. 2003; 362(9377):39–41. [PubMed: 12853198]
13. Dolwani S, Williams GT, West KP, et al. Analysis of inherited MYH/(MutYH) mutations in British Asian patients with colorectal cancer. Gut. 2007; 56(4):593. [PubMed: 17369389]
14. Jarvinen HJ, Peltomaki P. The complex genotype-phenotype relationship in familial adenomatous polyposis. Eur J Gastroenterol Hepatol. 2004; 16(1):5–8. [PubMed: 15095846]

15. Giardiello FM, Krush AJ, Petersen GM, et al. Phenotypic variability of familial adenomatous polyposis in 11 unrelated families with identical *APC* gene mutation. Gastroenterology. 1994; 106(6):1542–1547. [PubMed: 8194700]
16. Nieuwenhuis MH, Vasen HF. Correlations between mutation site in *APC* and phenotype of familial adenomatous polyposis (FAP): A review of the literature. Crit Rev Oncol Hematol. 2007; 61(2): 153–161. [PubMed: 17064931]
17. Schnitzler M, Koorey D, Dwight T, et al. Frequency of codon 1061 and codon 1309 APC mutations in Australian familial adenomatous polyposis patients. Hum Mutat. 1998; (Suppl 1):S56–S57. [PubMed: 9452041]
18. Gavert N, Yaron Y, Naiman T, et al. A. Molecular analysis of the APC gene in 71 Israeli families: 17 novel mutations. Hum Mutat. 2002; 19(6):664. [PubMed: 12007223]
29. Cao X, Eu KW, Seow-Choen F, et al. *APC* mutation and phenotypic spectrum of Singapore familial adenomatous polyposis patients. Eur J Hum Genet. 2000; 8(1):42–48. [PubMed: 10713886]
20. Han SH, Ryu JS, Kim YJ, et al. Mutation analysis of the *APC* gene in unrelated Korean patients with FAP: Four novel mutations with unusual phenotype. Fam Cancer. 2011; 10(1):21–26. [PubMed: 21110124]
21. National Comprehensive Cancer Network. Colorectal Cancer Screening (2.2013). http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf.
22. Shields AE, Burke W, Levy DE. Differential use of available genetic tests among primary care physicians in the United States: results of a national survey. Genet Med. 2008; 10(6):404–414. [PubMed: 18496223]
23. Armstrong K, Micco E, Carney A, et al. Racial differences in the use of BRCA1/2 testing among women with a family history of breast or ovarian cancer. JAMA. 2005; 293:1729–1736. [PubMed: 15827311]
24. Peters N, Rose A, Armstrong K. The association between race and attitudes about predictive genetic testing. Cancer Epidemiol Biomarkers Prev. 2004; 13:361–365. [PubMed: 15006909]
25. Case AP, Ramadhani TA, Canfield MA, et al. Awareness and attitudes regarding prenatal testing among Texas women of childbearing age. J Genet Couns. 2007; 16:655–661. [PubMed: 17674167]
26. Suther S, Kiros GE. Barriers to the use of genetic testing: a study of racial and ethnic disparities. Genet Med. 2009; 11(9):655–662. [PubMed: 19752639]
27. Kastrinos F, Steyerberg EW, Balmaña J, et al. Comparison of the clinical prediction model $PREMM_{1,2,6}$ and molecular testing for the systematic identification of Lynch syndrome in colorectal cancer. Gut. 2013; 62(2):272–279. [PubMed: 22345660]
28. Kastrinos F, Steyerberg EW, Mercado R, et al. The $PREMM_{1,2,6}$ model predicts risk of MLH1, MSH2, and MSH6 germline mutations based on cancer history. Gastroenterology. 2011; 140(1): 73–81. [PubMed: 20727894]

Table 1

Characteristics of Eligible Subjects (n=6169)

	n (%)
Male (%)	3086 (50%)
Ancestry/Race (%)	
Western European	4358 (70.6%)
Eastern European	413 (6.7%)
Ashkenazi	270 (4.4%)
Asian	151 (2. 5%)
African American	382 (6.2%)
Latin American/C aribbean	385 (6.2%)
Native American	69 (1.1%)
Near/Middle Eastern	48 (0.8%)
Other	93 (1.5%)
Age at first colorectal adenoma diagnosis (mean±SE)	45±.2
Adenoma count, No. (%)	
0	933 (15.1%)
<10	871 (14.1%)
10–19	726 (11.8%)
20–99	2477 (40.2%)
100–999	1066 (17.3%)
≥1000	96 (1.6%)
Age at CRC diagnosis (mean±SE)	46.5±.4
History of CRC (%)	
CRC and adenoma	1292 (20.9%)
CRC alone	368 (6.0%)
CRC (total)	1660 (27%)
First-degree relative with CRC (%)	1929 (31.3%)

Abbreviations: CRC, colorectal cancer

Table 2

Prevalence of Mutations Based on Race or Ethnicity

	Caucasian (n=5041)	Asian (n=151)	African American (n=382)	Other (n=595)	Total (n=6169)	P value
	n (%) 95% CI	n (%) 95% CI	n (%) 95% CI	n (%) 95% CI	n (%)	
Pathogenic mutation						
APC	782 (15.5%)	38 (25.2%)	118 (30.9%)	143 (24%)	1081 (17.5%)	<0.0001
	14.5–16.5	18.5–32.9	26.3–35.8	20.7–27.7		
Biallelic *MUT YH*	250 (5%)	4 (2.7%)	1 (0.3%)	43 (7.2%)	298 (4.8%)	<0.0001
	4.4–5.6	.7–6.6	0.01–1.5	5.3–9.6		
VUS						
APC	303 (6%)	17 (11.3%)	43 (11.3%)	36 (6.1%)	399 (6.5%)	<0.0001
	5.4–6.7	6.7–17.4	8.3–14.9	4.3–8.3		
MUTYH	39 (0.8%)	3 (2%)	12 (3.1%)	1 (0.2%)	55 (0.9%)	<0.0001[c]
	0.6–1.1	0.4–5.7	1.6–5.4	0–0.9		
No mutation[a]						
When tested for *APC*[b]	3956 (78.9%)	96 (63.6%)	221 (57.6%)	416 (68.7%)	4689 (74.6%)	<0.0001
	75.7–78	55.4–71.3	52.5–62.6	64.8–72.3		
When tested for *MUTYH*	4640 (92%)	143 (94.7%)	366 (95.8%)	537 (90.3%)	5686 (92.1%)	0.0092
	91.2–92.7	89.8–97.7	93.3–97.6	87.6–92.5		

Abbreviations: APC, adenomatous polyposis coli; VUS, variant of unknown significance Percentages represent column percentages

[a]No mutation is considered a nonpathogenic polymorphism or no detected gene alteration

[b]The APC 1307K polymorphism was noted in 55 Caucasians, 0 Asians or African Americans, and 3 subjects of Other race/ethnicity

All statistical analyses were performed using a χ^2 test except where indicated (Fisher's exact test indicated by [c])

Table 3

Detection of Biallelic MUTYH Mutations by Type of DNA Mutational Analysis Based on Race or Ethnicity

	***MUTYH* panel[a] or full analysis after positive *MUTYH* panel**	**Full *MUTYH* sequencing**	**P value**
	n (%)	**n (%)**	
Caucasian biallelic *MUTYH* mutation	239 (5%) (239/4526)	11 (2%) (11/515)	0.002
Non-Caucasian biallelic *MUTYH* mutation	31 (3%) (31/965)	17 (2%) (17/163)	<0.0002

[a]MUTYH panel is defined as testing for Y179C and G396D only

Table 4

Comparison of Adenoma Characteristics at Referral Based on Race or Ethnicity

	Caucasian (n=5041)	Asian (n=151)	African American (n=382)	Other (n=595)	P value
	n (%) 95% CI	n (%) 95% CI	n (%) 95% CI	n (%) 95% CI	
Age at adenoma diagnosis mean± SE, 95% CI	45.4±.2	43.5±1.1	43.9±.7	42.9±.6	<0.0001
	45–45.8	41.2–45.7	42.5–45.2	41.8–44	
0 adenomas	762 (15.1%)	20 (13.3%)	42 (11%)	109 (18.3%)	0.0168
	14.1–16.1	8.3–19.7	8–14.6	15.3–21.7	
≤10 adenomas	732 (14.5%)	23 (15.2%)	42 (11%)	74 (12.4%)	0.15
	13.6–15.5	9.9–22	8–14.6	9.9–15.4	
11–19 adenomas	607 (12%)	11 (7.3%)	54 (14.1%)	54 (9.1%)	0.02
	11.2–13	3.7–12.7	10.8–18	6.9–11.7	
20–99 adenomas	2064 (40.9%)	57 (37.8%)	140 (36.7%)	216 (36.3%)	0.06
	39.6–42.3	30–46	31.8–41.7	32.4–40.3	
100–999 adenomas	805 (16%)	33 (21.9%)	95 (24.9%)	133 (22.4%)	<0.0001
	15–17	15.6–29.3	20.6–29.5	19–25.9	
≥1000 adenomas	71 (1.4%)	7 (4.6%)	9 (2.4%	9 (1.5%)	0.0086
	1.1–1.8	1.9–9.3	1.1–4.4	0.7–2.9	

Continuous data were analyzed using ANOVA. Categorical data were analyzed using a χ^2 test. 95% confidence intervals of proportions presented with each value.

Table 5

Comparison of Colorectal Cancer Characteristics at Referral Based on Race or Ethnicity

	Caucasian (n=5041)	Asian (n=151)	African American (n=382)	Other (n=595)	P value
	n (%) 95% CI	n (%) 95% CI	n (%) 95% CI	n (%) 95% CI	
Age at CRC diagnosis mean± SE, 95% CI	47.3±.4	44.7±2	44.6±1.3	41.7±1.2	<0.0001
	46.5–48.1	40.7–48.6	42–47.3	39.4–44	
CRC and adenoma	1031 (20.5%)	41 (27.2%)	90 (24%)	130 (21.9%)	0.11
	19.4–21.6	20.2–35	19.4–28.1	18.6–25.4	
CRC alone	302 (6%)	11 (7.3%)	16 (4.2%)	39 (6.6%)	0.39
	5.4–6.7	3.7–12.7	2.4–6.7	4.7–8.9	
First-degree relative with CRC	1563 (31%)	38 (25.2%)	138 (36.1%)	190 (31.9%)	0.07
	29.7–32.3	18.5–32.9	31.3–41.2	28.2–35.9	

Continuous data were analyzed using ANOVA. Categorical data were analyzed using a χ^2 test. 95% confidence intervals of proportions presented with each value.