Published in final edited form as:

Fam Cancer. 2013 September ; 12(3): 555–562. doi:10.1007/s10689-013-9617-z.

Clinical characterization and mutation spectrum in Hispanic families with adenomatous polyposis syndromes

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Abstract

Background—Several genetically defined hereditary CRC syndromes are associated with colonic polyposis including familial adenomatous polyposis (FAP) and MUTYH adenomatous polyposis (MAP). Limited data exists on the clinical characterization and genotypic spectrum of polyposis syndromes among Hispanics.

Purpose—To describe the phenotype and genotype of Puerto Rican Hispanic patients with FAP and MUTYH and compare with other ethnic and racial groups.

Methods—Probands were identified from the Puerto Rico Familial Colorectal Cancer Registry (PURIFICAR). Recruited individuals completed risk factors, medical, and family history questionnaires and underwent genetic testing for genotype analysis. Frequency analysis, chi-square, Fisher's exact test and Wilcoxon rank-sum test were used for statistical analysis methods.

Results—A total of 31 FAP (from 19 families) and 13 MAP (from 13 families) Hispanic patients recruited from the Puerto Rico Familial Colorectal Cancer Registry were evaluated. Among the FAP cases, mean age at diagnosis was 27.6 (range 9–71 years); 67.7% cases had more than 100 polyps and 41.9% had upper gastrointestinal polyps. Among the 19 FAP families, there were 77 affected FAP individuals and 26 colorectal cancer cases. Genetic mutations were available for 42.2% of FAP families; all mutations identified were unique. Surgeries were reported in 31 cases; 14 (45.2%) prophylactic surgeries and 6 (19.4%) therapeutic surgeries for management of CRC. Among MAP cases, mean age at diagnosis was 53 (range 34–76 years) and genetic analysis revealed homozygous biallelic mutations (G382D) in 53.8%, compound heterozygous mutations (G382/Y165C) in 23%, and non-G382/Y165C monoallelic mutations in 23%.

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Disclosures—None of the authors have any commercial conflicts to disclose.

Conclusions—Familial cancer registries should be promoted as vehicles for detection, education and follow up of families at-risk of acquiring familial cancers. PURIFICAR is the first and only familial cancer registry in Puerto Rico providing these services to families affected with familial cancer syndromes promoting education, testing and surveillance of at-risk family members, and focusing on cancer prevention efforts. The fact that only 40% of FAP patients had access to genetic testing stresses the need to promote the establishment of policies supporting genetic testing coverage by medical insurance companies in order to provide patients with the highest standard of care to prevent cancer. Furthermore, our results suggest that Hispanics may have uncommon mutations in adenomatous polyposis related genes, which emphasize the need for full gene sequencing to establish genetic diagnosis.

Keywords

familial adenomatous polyposis; MUTYH (Mut Y Homologue); family registry; Hispanics

Introduction

In Puerto Rico, colorectal cancer (CRC) represents the second leading cause of cancer in men and women [17]. Familial CRC accounts for 10–15% of all CRCs [10, 12] and several studies suggest that inheritance has a significant impact in the pathogenesis of up to a third of all CRC cases [8,9]. One such familial syndrome accounting for about 1% of all CRC cases is familial adenomatous polyposis (FAP) [1]. However, little is known about the prevalence, clinical manifestations and genetic mutations in US Hispanic individuals with familial polyposis syndromes.

Familial adenomatous polyposis is an autosomal dominant inherited disease that usually manifests as tens to thousands of adenomas in the colon and rectum in the second decade of life. These patients have a 100% risk of developing CRC, which usually occurs a decade after adenomas first present [1]. FAP occurs in 1 out of every 8,300 people (1). Patients often go without symptoms for years until adenomas become so numerous and large that they manifest as nonspecific symptoms such as anemia, rectal bleeding, abdominal pain, constipation or diarrhea, palpable abdominal masses and weight loss [1]. Aside from CRC, FAP usually manifests with benign or malignant extracolonic abnormalities including osteomas, dental abnormalities, congenital hypertrophy of the retinal pigment epithelium, desmoids tumors and extra-colonic malignancies in the thyroid, liver, bile ducts and central nervous system [1]. Additionally, FAP presents with extracolonic polyps in the duodenum and the stomach [14]. FAP results from a germline mutation in the Adenomatous Polyposis Coli (APC) gene. Most patients (70%) have a family history of CRC [1].

Other individuals with adenomatous polyposis present with an autosomal recessive disorder and have a MUTYH mutation that causes MUTYH-associated polyposis (MAP). The MUTYH gene codes for an enzyme involved in DNA that repairs oxidative damage [18]. The two most common variants in the MUTYH gene are Y165C and G382D missense mutations, both accounting for more than 80% of all MYH variants reported in Caucasian populations. When an individual inherits two copies of a defective MUTYH gene, they inherit the familial cancer syndrome, MAP. This autosomal recessive condition is characterized by an increased risk of developing CRC and adenomas in both the upper and lower gastrointestinal tract [1].

The aim of the present study is to characterize the phenotype (including colonic and extra-colonic manifestations) and genotype (APC/MUTY genes) of US Hispanics individuals with polyposis syndromes recruited to the Puerto Rico Familial Colorectal Cancer Registry (PURIFICAR).

Methods

Individuals with either personal or family history of possible familial colorectal cancer and/or polyposis are referred to the Puerto Rico Familial Colorectal Cancer Registry (PURIFICAR; <http://purificar.rcm.upr.edu/>) [13] by gastroenterologists, oncologists, and colorectal surgeons. The Puerto Rico Central Cancer Registry (PRCCR), the state funded national cancer registry in Puerto Rico, also refers incident colorectal cancer cases to PURIFICAR. The probands in this study were identified from PURIFICAR (<http://purificar.rcm.upr.edu/>) [13]. PURIFICAR was established in 2005 at the University of Puerto Rico Comprehensive Cancer Center and has received direct or in kind support from the National Institutes of Health, the Puerto Rico Gastroenterology Association and the Puerto Rico Colorectal Cancer Coalition (see Acknowledgment Section). Subjects enrolled in PURIFICAR are US Hispanic individuals with a clinical and/or genetic diagnosis of FAP, attenuated FAP (AFAP), MAP, hamartomatous polyposis syndromes and Lynch Syndrome. Consented probands complete a comprehensive baseline questionnaire capturing medical, environmental exposures and cancer family history. Probands are referred to the Hereditary Cancer Prevention Clinic (led by Dr. Marcia Cruz-Correa) where they are offered a vast array of services including but not limited to genetic counseling and testing, diagnostic and surveillance endoscopic, radiographic and/or surgical procedures, referral to specialists, and communication with insurance companies to facilitate coverage/approval of services (Figure 1).

Pedigrees for each proband are completed to trace the number of affected relatives with polyposis and/or cancer using PROGENY [21]. Pathology reports and medical/surgical records are obtained to confirm cancer diagnosis reported by probands. Affected family members living in Puerto Rico and US are also invited to participate in the registry.

Our study population consists of US Hispanic men and women ages 10 and older recruited through PURIFICAR. For the current study, analysis was limited to cases with both the clinical and/or genetic diagnosis of FAP and cases with genetic diagnosis of MAP. Genetic diagnosis of FAP and MAP was established by identifying mutations by commercial sequence analyses (MYRIAD Genetic Laboratories, Inc.) of the *APC* and *MUTYH* genes, respectively. Clinical diagnosis of FAP was defined as individuals with more than 20 neoplastic lesions taking into account age at onset and inheritance pattern (adenomas). All patients were ruled out for *APC* mutations prior to undergoing *MUTYH* sequence analysis.

The statistical analyses consisted of frequency distribution, Wilcoxon rank-sum test, chi-square, Fisher's exact test as appropriate using STATA 11.0 software (STATA Corporation, Texas) [22].

Results

We report for the first time observations on Hispanics with familial polyposis syndrome recruited through the Puerto Rico Familial Colorectal Cancer Registry (PURIFICAR) [13]. Data from familial cancer registries have been reported previously in other populations, however, no data have been reported from a predominantly Hispanic population.

Familial Adenomatous Polyposis (FAP)

A total of 31 Hispanic cases representing 19 families with the clinical and/or genetic diagnosis of FAP with a mean age of 27.6 (range 9–71 years) and 51.6% male are reported. The clinical characteristics of FAP patients are summarized in Table 1. We detected 100 colorectal polyps in 21 (67.7%) of cases, while upper gastrointestinal polyps were detected in 13 (41.9%) of individuals. Data regarding benign extracolonic manifestations was not

available for all our cases; however, 3 (9.7%) had osteomas 3(6.5%) epidermal cysts, and none had thyroid nodules. Desmoid tumors were detected in three cases (9.7%) in two families (Family IDs: 8521 & 9132); no cases of duodenal or thyroid cancer were identified in our cohort.

Among the 19 FAP families in our study, there were 77 affected FAP individuals and 26 colorectal cancer cases. Data on the number of affected individuals per family and genetic mutation is summarized in Table 2. During the evaluation of each family we contacted over 100 relatives (an average of 5 relatives/family). Genetic counseling/testing was offered for at risk first-degree relatives when the family mutation was available. Of the 19 families included, data on genetic mutation was only available for 42.2% of families the remaining FAP diagnoses were based on clinical phenotypes of adenomatous polyposis and a positive family history exhibiting autosomal dominant pattern. All mutations identified within our cohort were unique for each family. Of the 31 FAP cases, 13 (41.9%) had prophylactic surgery and 6 (19.4%) had therapeutic surgery after the diagnosis of colorectal cancer. Of those opting for prophylactic surgery, 36% had an ileorectal anastomosis (IRA), 64% an ileoanal pouch anastomosis (IPAA). Among those receiving therapeutic surgeries for CRC, 17% received an IRA, while 83% received an IPAA.

MUTYH Associated Polyposis (MAP)

A total of 13 cases representing 13 families with genetic diagnosis of MAP and mean age at diagnosis of 53 years (range 34–76 years); 30.8% males, are reported. The clinical characteristics of the MAP patients are summarized in Table 1. We detected 100 colorectal polyps in 4 (30.8%) cases, while upper gastrointestinal polyps were detected in 4 individuals. Regarding benign extra-colonic manifestations 1 patient had epidermal cysts, 4 were found to have thyroid nodules, and none were found to have osteomas or CHRPE. No patients had extracolonic malignant cancers such as desmoid, duodenal or thyroid cancer.

Among the 13 MAP families in our registry, there were 19 affected individuals and 2 colorectal cancer cases. Data on the number of affected individuals and genetic mutations are summarized in Table 2. Genetic mutation status was available on 100 % of families, with 46.2% carrying homozygous biallelic mutations for G382D, 23.1% with compound heterozygous mutations (G382/Y165C), and 30.8% with monoallelic mutations. Although 30.8% of our cases had monoallelic mutations, they presented with a less aggressive phenotype comparable to some of the cases with biallelic *MUTYH* mutations. Polyp counts in these individuals ranged from 5–20 polyps (9215: 5 polyps; 9185: 10 polyps; 9150: 13 polyps; and 9255: 20 polyps) and they had no extra intestinal manifestations.

Of our 13 MAP cases, 3 (23.1%) had prophylactic surgeries. Of the three cases opting for prophylactic surgery, 1 had an IRA and 2 an IPAA, all had >100 polyps. Two of the probands presented with CRC, but only one therapeutic IRA surgery had been done by the time our study concluded. In comparison with the high percentage of our FAP cases, which undergo prophylactic surgery, *MUTYH* cases are primarily being followed clinically.

Discussion

PURIFICAR is the first familial cancer registry established in Puerto Rico. We report, for the first time to our knowledge, clinical and genetic mutation data from a Hispanic population with familial polyposis (44 cases from 32 families). Clinical and genetic data from familial polyposis registries (ranging from 77–122 patients; representing 33–96 families) have been previously reported in most Caucasian cohorts [3–6]. Our Hispanic cases had similar prevalence of colorectal and gastrointestinal polyps as noted in other non-Hispanic cohorts [4]. Extracolonic malignancies were found in 9.1% of our cohort, similar

to that observed in other reported familial polyposis registries [6,15]. However, our findings emphasize the need to further evaluate genotypic and phenotypic data in familial cancer syndromes in other ethnic groups in order to make the best screening and testing strategies for at-risk patient management.

A total of 31 FAP cases from 19 families recruited from PURIFICAR were evaluated in this study. In contrast to other studies, we found a lower mean age at diagnosis (27 vs. 32–41 years), which may be possibly due to our inclusion of younger patients [3–6]. Unique genetic mutations were detected in the 42.2% of FAP families for which insurance companies provided coverage for genetic testing. The remaining 57.8% families had a clinical diagnosis of FAP. The fact that we are not able to provide germline mutation analyses to all patients represents a limitation of this study as some FAP patients may actually have MAP. However, the higher polyp burden observed in most patients classified as FAP (with over two-thirds having more than 100 colonic adenomas), the earlier age of onset (mean age at diagnosis 27 years of age) and the autosomal dominant inheritance pattern observed in the affected families support the FAP diagnosis. Extracolonic malignancies are not uncommon in patients with FAP. Previously, published studies report a prevalence of 25%–66% for congenital hypertrophy of the retinal pigment epithelium (CHRPE) among FAP cases; however, there were no available data for this condition within our study [5]. Limited use of routine ophthalmic examination of FAP individuals and/or non-referral of CHRPE-positive patients for genetic evaluation may be contributing factors to our observations. Data regarding benign extracolonic manifestations was not available for all our cases; however, 41.9% patients had upper gastrointestinal, 9.7% had osteomas, 6.5% epidermal cysts, and none had thyroid nodules. Desmoid tumors were detected in three cases (9.7%) in two families (Family IDs: 8521 & 9132); no cases of duodenal or thyroid cancer were identified in our cohort. We observed that a third of our FAP cases had prophylactic IRA. In contrast, 90% of prophylactic surgeries performed during the last decade were IPAA, which may reflect surgical trends and available technical expertise. Regarding prophylactic colorectal surgeries, less restorative proctocolectomies were performed in our Hispanic FAP patients compared to other populations (57% vs. 73%)[3].

Limited studies exist evaluating MAP cohorts regarding mutation and clinical spectrum. One investigation included 26 patients from 9 families with a mean age of diagnosis of 47 years (range 30–70 years) for patients with biallelic *MUTYH* mutations, with 11.5% of these patients having more than 100 colonic polyps [20]. Our data are similar to most previous studies in Caucasian populations with common biallelic *MUTYH* mutations variants (Y165C and G382D variants also known as Y179C and G396D) accounting for more than 80% of all reported mutant alleles [18]. There is very limited information on particular *MUTYH* sequence variants in racial/ethnic groups other than Caucasians [18, 23]. In our Hispanic cohort, we identified *MUTYH* variants not routinely seen among the Caucasian cohorts, which would have resulted in the failure to identify MAP in several Hispanic patients if only the *MUTYH* variants Y165C and G382D were tested. Hispanics are an admixed population resulting from the mixture of three races (European, African and Indian), which may account for the unusual *MUTYH* variants found in our cohort. Our results support the need for a more comprehensive characterization of the mutations associated with MAP in other racial/ethnic groups and the use of full *MUTYH* sequencing in non-Caucasian individuals.

A striking finding in our cohort was that 30.8% of the MAP patients had monoallelic *MUTYH* mutations. Individuals who inherit both *MUTYH* mutations develop the clinical phenotype of MAP. However, it is unclear whether carriers of only one mutation (monoallelic variants) are at increased risk for CRC [18, 25–28]. This uncertainty is largely due to the low frequency of monoallelic carriers for *MUTYH* (1–2%) [1,18]. The frequency

of biallelic mutation carriers, on the other hand, is between 1 per 10,000 and 1 per 40,000 births (compared to 1 per 8,300 for FAP) [1]. Individuals with biallelic *MUTYH* mutations usually develop between 10 and 100 adenomas in the colon and rectum, and approximately one third develop adenomas in the upper GI tract. Among MAP Hispanic patients with biallelic mutations, we observed a similar frequency of gastrointestinal adenomas as seen in Caucasian cohorts, with most patients (93%) having < 100 colorectal adenomas and about a third (31%) having upper GI tract polyps. Some studies support that the number of adenomas are dependent on the number of mutated alleles in the *MUTYH* gene [24]. In our cohort, the monoallelic *MUTYH* mutation carriers presented a less aggressive phenotype with less than 20 polyps (ranging from 5–20 polyps) with no extra-intestinal manifestations. However, three out of the four probands had first-degree family members with adenomatous polyps whereas the other proband had two third-degree relatives with CRC at a young age (50 and 51 years of age). Although three of the four monoallelic mutations detected are not in the mutation hotspots, they may have the potential to adversely affect protein function which cannot be established solely based on sequence analyses. As genetic data from various racial/ethnic populations is still limited, it is vital to request a full DNA sequence of the *MUTYH* gene when evaluating non-Caucasian patients with polyposis.

MAP is a relatively newly recognized familial polyposis syndrome, therefore there is very limited information regarding cancer risk in these patients [1,18,23–29]. Biallelic *MUTYH* mutations have been reported to be associated with a 93-fold excess risk of CRC, with an almost complete penetrance at 60 years of age [27]. In addition, heterozygous and homozygous *MUTYH* mutation carriers were found to have a high risk for synchronous cancers (24% in the colorectum and 16% in the upper gastrointestinal tract), but did not show an increased risk for extra intestinal tumors [25]. Colorectal cancer risk among monoallelic mutation carriers still remains controversial. One meta-analysis showed that *MUTYH* mutation carriers had a slightly increased chance of CRC of 15% [18], while a Swiss cohort reported a significantly increased risk only for biallelic mutation carriers (71.4% vs. 0%, $p < 0.007$) [24]. Similarly, a large Spaniard population-based study reported no increased risk for CRC (odds ratio, 1.11; 95% confidence interval, 0.90–1.37) among monoallelic *MUTYH* carriers [29]. Only two individuals, biallelic *MUTYH* mutation carriers developed cancer during our study.

In Puerto Rico, diagnosis of familial polyposis syndromes is mainly based on clinical phenotype. In fact, genetic mutation analysis was only available for 42.2% of FAP families whereas the availability of genetic mutation results in other studies ranged from 24.0%–92.6% [3–6]. Barriers to genetic testing include lack of insurance coverage, limited awareness by physicians and patients, and cultural beliefs regarding colorectal cancer and genetic diseases. Mutation analysis of the *MUTYH* and *APC* genes is costly and not covered by most health insurance companies in Puerto Rico unless the patient has been diagnosed with CRC. All of the MAP patients were subjected to genetic testing due to the late-onset of the disease and the fact that Medicare covers these types of tests. The earlier onset of FAP and non-coverage of the genetic tests by their corresponding medical insurance companies resulted in relying on a clinical FAP diagnosis in 57.8% of the individuals in our study. Since identification of mutation-positive individuals results in early detection, improved cancer surveillance and decreased mortality, insurance coverage for genetic testing is imperative for the evaluation and management of individuals with GI polyposis and their at-risk relatives [2, 12]. More intensive efforts to educate healthcare providers, policy makers and the general public in the proper use of genetic testing for hereditary cancer syndromes are needed.

Recommendations

Having a first-degree relative with CRC increases a person's chance of developing CRC by 2–3 fold over the general population [10, 11]. In families with multiple relatives or younger relatives with CRC, the risk is even greater. This is especially important for FAP patients who have a 100% lifetime risk of acquiring CRC and increased risk of acquiring extracolonic cancers. The diagnosis, surveillance, early detection and systematic follow-up of these patients are of utmost importance. Diagnosis of polyposis syndromes is usually done through family history, physical examination, and procedures, such as colonoscopies, that look at the colon and rectum. FAP patients can be recognized easily during colonoscopy and this examination should be considered in patients with 10 or more colorectal adenomas. When 20 or more adenomas are present in the colon or rectum, these patients should be referred for genetic testing and mutation analysis of the polyposis genes: *APC* or *MUTYH* [1, 12].

When a germline *APC* mutation is identified in a family, all first-degree relatives of the index patient (proband) should be referred for genetic counseling and offered genetic testing because each family member carries a 50% chance of having the mutation [1]. In pedigrees with a diagnosed individual that has undergone genetic testing, other family members can be tested using a single site mutation analysis, which is a more affordable option. Knowing they carry a mutated *APC* or *MUTYH* gene gives individuals the opportunity to reduce their cancer risk or decrease the development of a second cancer [2]. When an *APC* mutation is detected in a family, all first-degree family members should be tested to receive proper counseling regarding their choices for cancer prevention and follow-up. These choices include prophylactic surgical resection of the colon starting during the second decade of life and beyond.

Evaluating family history during primary care visits is crucial and should become part of every cancer-screening program [12]. A thorough examination of family history includes collecting information regarding family size, number of first and second-degree relatives with cancer and type of cancer and age of diagnosis [12]. This allows identification of high-risk groups and also embarks these groups on more rigorous surveillance algorithms characterized by more frequent examinations starting at an early age [12]. Primary care physicians should be encouraged to refer patients for genetic counseling if there is a history of 2 or more family members diagnosed with CRC and/or one family member is diagnosed with CRC before 50 years of age [12]. Familial Cancer registries are of the utmost importance as it facilitates identification of high-risk families and provides the infrastructure to promote education among probands and relatives regarding cancer risk and risk-reduction strategies [7].

Acknowledgments

This publication was possible by Award Number U54 RR026139 from the National Center for Research Resources, and the Award Number 8U54MD 007587-03 from the National Institute on Minority Health and Health Disparities; and from award K22 CA115913 from the National Cancer Institute. PURIFICAR was partially supported by award 5R03CA130034-02 from the National Cancer Institute and the University of Puerto Rico Comprehensive Cancer Center. The authors are grateful to members of the Puerto Rico Coalition Coalicion (C3PR) and the Puerto Rico Gastroenterology Association (PRGA; www.gastropr.org) including Dr. Rafael Mosquera (President-Elect C3PR) and Dr. Suzette Rivera McMurray (President PRGA), respectively. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Half E, Bercovich D, Rozen P. Familial adenomatous polyposis. *Orphanet Journal of Rare Diseases*. 2009; 4:22. [PubMed: 19822006]

2. Myriad. Polyposis Syndromes. Retrieved February 14, 2012, from http://www.myriadtests.com/index.php?page_id=122
3. Chew MH, Quah HM, Teh KL, Loi TT, Eu KW, Tang CL. Twenty years of familial adenomatosis syndromes in the Singapore Polyposis Registry: an analysis of outcomes. *Singapore Med J*. 2011; 52(4):246. [PubMed: 21552784]
4. Kanter-Smoler G, Fritzell K, et al. Clinical characterization and the mutation spectrum in Swedish adenomatous polyposis families. *Bio Med Central*. 2008; 6:10.
5. Garzón-Benavides M, Pizarro-Moreno A, García-Lozano R, Herrero-Garrido MI, Hervás-Molina AJ, Márquez-Galán JL, Cordero-Fernández C. Andalusian Registry for Familial Adenomatous Polyposis. Analysis of patients included. *Revista Espanola de Enfermedades Digestivas*. 2010; 102(11):653–657. [PubMed: 21142386]
6. Truta B, Allen BA, Conrad PG, Weinberg V, Miller GA, Pomponio R, Lipton LR, Guerra G, Tomlinson IP, Sleisenger MH, Kim YS, Terdiman JP. A comparison of the phenotype and genotype in adenomatous polyposis patients with and without family history. *Familial Cancer*. 2005; 4:127–133. [PubMed: 15951963]
7. Groombridge C, Burgess B, Spigelman AD, O'Toole L. Disseminating risk information to familial adenomatous polyposis families. *Familial Cancer*. 2007; 6:323–324. [PubMed: 17333476]
8. Cannon-Albright LA, Skolnick MH, Bishop DT, Lee RG, Burt RW. Common inheritance of susceptibility to colonic adenomatous polyps and associated colorectal cancers. *N Engl J Med*. 1988; 319(9):533–537. [PubMed: 2841598]
9. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer: analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med*. 2000; 343:78–85. [PubMed: 10891514]
10. Burt RW. Colon Cancer screening. *Gastroenterology*. 2000; 119 (3):837–853. [PubMed: 10982778]
11. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. *Am J Gastroenterol*. 2001; 96(10):2992–3003. [PubMed: 11693338]
12. Vasen HF, Möslein G, Alonso A, et al. Recommendations to improve hereditary and familial colorectal cancer in Europe. *Familial Cancer*. 2010; 9:109–115. [PubMed: 19763885]
13. Puerto Rico Familial Colorectal Cancer Registry. Retrieved February 12, 2012 from http://purificar.rcm.upr.edu/index_eng.html
14. Spigelman AD. Extracolonic polyposis in familial adenomatous polyposis: so near and yet so far. *Gut*. 2004 Mar; 53(3):381–386. [PubMed: 14960520]
15. Campos, FG.; Habr-Gama, A.; Kiss, DR.; Atuí, FC.; Katayama, F.; Gama-Rodrigues, J. *Arq Gastroenterol*. Vol. 40. São Paulo; 2003. Extracolonic manifestations of familial adenomatous polyposis: incidence and impact on the disease outcome.
16. Enomoto M, Konishi M, Iwama T, Utsunomiya J, Sugihara KI, Miyaki M. The relationship between frequencies of extracolonic manifestations and the position of APC germline mutation in patients with familial adenomatous polyposis. *Jpn J Clin Oncol*. 2000; 30(2):82–88. [PubMed: 10768871]
17. Puerto Rico Central Cancer Registry. Age-Adjusted Incidence Rates of Colorectal Cancer, Puerto Rico 2004–2008. 2011 Dec. Puerto Rico Preliminary Incidence File
18. Win AK, Hopper JL, Jenkins MA. Association between monoallelic MUTYH and colorectal cancer risk: a meta-regression analysis. *Familial cancer*. 2011; 10:1–9. [PubMed: 21061173]
19. Cruz-Correa M, Giardiello FM. Familial adenomatous polyposis. *Gastrointestinal Endoscopy*. 2003; 58:885–894. [PubMed: 14652558]
20. Nielsen M, Hes FJ, Nagengast FM, Weiss MM, Mathus-Vliegen EM, Morreau H, Breuning MH, Wijnen JT, Tops CM, Vasen HF. Germline mutations in APC and MUTYH are responsible for the majority of families with attenuated familial adenomatous polyposis. *Clinical Genetics*. 2007; 71:427–433. [PubMed: 17489848]
21. Progeny (Version 4.5.02) [Software]. Progeny Software, LLC; 2002. Retrieved from <http://www.progenygenetics.com/>
22. Stata/SE (Version 10.0) [Software]. College Station, TX: Stata Corp LP; 1985. Retrieved from <http://www.stata.com>

23. Isidro G, Laranjeira F, Pires A, et al. Germline MUTYH (MYH) mutations in Portuguese individuals with multiple colorectal adenomas. *Hum Mutat.* 2004; 24:353–354. [PubMed: 15366000]
24. Russell AM, Zhang J, Luz J, et al. Prevalence of *MYH* germline mutations in Swiss *APC* mutation-negative polyposis patients. *Int J Cancer.* 2006; 118:1937–1940. [PubMed: 16287072]
25. Olschwang S, Blanché H, de Moncuit C, Thomas G. Similar colorectal cancer risk in patients with monoallelic and biallelic mutations in the MYH gene identified in a population with adenomatous polyposis. *Genet Test.* 2007; 11(3):315–20. [PubMed: 17949294]
26. Croitoru ME, Cleary SP, Di Nicola N, et al. Association between biallelic and monoallelic germline MYH gene mutations and colorectal cancer risk. *J Natl Cancer Inst.* 2004; 96:1631–1634. [PubMed: 15523092]
27. 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; 77:1. [PubMed: 15931593]
28. Webb EL, Rudd MF, Houlston RS. Colorectal cancer risk in monoallelic carriers of MYH variants. *Am J Hum Genet.* 2006; 79:768–771. [PubMed: 16960817]
29. Balaguer F, Castellví-Bel S, Castells A, et al. Gastrointestinal Oncology Group of the Spanish Gastroenterological Association. Identification of MYH mutation carriers in colorectal cancer: a multicenter, case-control, population-based study. *Clin Gastroenterol Hepatol.* 2007; 5(3):379–387. [PubMed: 17368238]

Figure 1. PURIFICAR recruitment and retention algorithm

* The Puerto Rico Central Cancer Registry only referred colorectal cancer cases.

Table 1

Characteristics of adenomatous polyposis in patients with FAP and MAP

Clinical Characteristics	<u>Familial polyposis syndrome</u>		P-value
	FAP	MUTYH	
Number of recruited cases	31	13	
Sex, n(%)			0.205 ^c
Male	16 (51.6)	4 (30.8)	
Female	15 (48.4)	9 (69.2)	
Mean age at diagnosis (range)	27.61 (9–71)	53.08 (34–76)	0.0001 ^b
No. of polyps			0.010 ^a
5–20	3 (9.7)	5 (38.5)	
21–50	1 (3.2)	3 (23.1)	
51–100	6 (19.4)	1 (7.7)	
>100	21 (67.7)	4 (30.8)	
Colorectal cancer, n(%)	7 (22.6)	2 (15.4)	0.703 ^a
Upper gastrointestinal polyps, n (%)	13 (41.9)	4 (30.8)	0.488 ^c
Benign extracolonic manifestations, n (%)			
Osteoma	3 (9.7)	0 (0)	0.544 ^a
Epidermal cysts	2 (6.5)	1 (7.7)	>0.99 ^a
Thyroid nodules	0 (0)	4 (30.8)	0.005 ^a

^aFisher's Exact Test^bWilcoxon Rank-sum Test^cPearson Chi-Square

Table 2

Genetic mutations and colorectal cancer in FAP/MAP families*

FAP			
Study ID	APC Genetic Mutation	# of known affected individuals per family	# of CRC cases per family
8128	Clinical Diagnosis	3	1
9248	Clinical Diagnosis	3	1
GMV	Clinical Diagnosis	6	0
9128	IVS8 +2T>C	12	9
9121	Clinical Diagnosis	6	4
9050	Clinical Diagnosis	14	5
9148	3183del 5	2	0
9132	4612 del GA	2	0
9250	3149delC	12	1
8378	Clinical Diagnosis	1	0
8379	Clinical Diagnosis	1	0
8389	Clinical Diagnosis	3	2
8405	3927DEL5	1	0
8521	Clinical Diagnosis	2	1
9076	Clinical Diagnosis	1	1
9157	Clinical Diagnosis	1	1
10391007	4035insA (deleterious)	4	0
10391008	Q625X (1873C>T)	2	0
10391015	Q1338X (4012C>T)	1	0

MUTYH			
Study ID	MUTYH Genetic Mutation	# of known affected individuals per family	# of CRC cases per family
8496	G382D (1145G>A), 2 copies	2	1
9254	G382D (1145G>A), 2 copies	1	1
9138	G382D (1145G>A), 2 copies	2	1
9169	G382D (1145G>A), 2 copies	2	1
9221	G382D (1145G>A), 2 copies	1	0
9195	G382D (1145G>A) - Y165C (494A>G)	1	0
9175	G382D (1145G>A) - Y165C (494A>G)	2	0
9177	G382D (1145G>A) - Y165C (494A>G)	1	0
9129	G382D (1145G>A), 2 copies	1	0
9150	G382D (1145G>A), 1 copy	1	0
9185	N42S (125 A>G), 1 copy	1	0
9217	E465del (1395del3), 1 copy	3	0
9255	IVS7 + 8G>C; 1 copy	1	0

* Families include proband.