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ORIGINAL ARTICLE

Frequency of the common germline *MUTYH* mutations p.G396D and p.Y179C in patients diagnosed with colorectal cancer in Southern Brazil

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Abstract
Introduction *MUTYH*-associated polyposis (MAP) is an autosomal recessive cancer predisposition syndrome associated with the development of colorectal tumors and colonic polyps at an early age. MAP syndrome is associated to germline biallelic mutations in the *MUTYH* gene which lead to deficient DNA repair through the base-excision repair system and accumulation of G:C→T:A transversions. Occurrence of such mutations in oncogenes and tumor suppressor genes drives colorectal carcinogenesis and is associated with the development of colonic polyps. Two common mutations, p.Y179C and p.G396D, are present in approximately 70–80% of MAP in European families with identified *MUTYH* germline mutations. The aim of this study was to assess the frequency of the germline *MUTYH* mutations p.Y179C and p.G396D in Brazilian patients with MAP and other hereditary colorectal cancer (CRC) phenotypes, as well as in sporadic CRC cases.
Materials and methods A total of 75 patients were included. Samples were screened for the *MUTYH* germline mutations p.Y179C and p.G396D by allelic discrimination assays using allele-specific TaqMan® probes. In all mutation-positive cases, results were confirmed by sequencing.
Results and conclusions Biallelic germline *MUTYH* mutations were identified in 4 of 60 (6.6%) patients with a phenotype of hereditary colorectal cancer. Germline *MUTYH*

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mutation screening should be considered in the differential diagnosis of hereditary colorectal syndromes, and not only in MAP, but also in familial adenomatous polyposis and Bethesda criteria-positive families. Additional mutation screening studies of the *MUTYH* gene in a larger number of Brazilian patients will be necessary to confirm these results and determine the validity and applicability of *MUTYH* mutation screening in our population.

Keywords *MUTYH* mutations · Colorectal cancer · *MUTYH*-associated polyposis

Introduction

The *MUTYH* gene (MutY human homologue), localized at 1p34.2-1p33, is a member of the base-excision repair pathway and its product, the mutyh protein, is directly involved in the repair of oxidative DNA damage, especially that caused by oxidation of guanine to 8-oxo-7,8-dihy-dro-2-deoxyguanosine (8-oxoG) [1, 2]. Biallelic loss of function mutations in *MUTYH* lead to increased G:C→T:A transversions in oncogenes and tumor suppressor genes, such as *KRAS* and *APC*, that play a central role in cellular proliferation of the colorectum [1]. The accumulation of somatic mutations in these and other genes related to colorectal carcinogenesis leads to the rapid development of colonic tumors. The occurrence of germline biallelic mutations in *MUTYH* is associated with the *MUTYH*-associated polyposis (MAP) syndrome (OMIM# 608456), first described in 2002 [3].

MAP is an autosomal recessive cancer predisposition syndrome associated with the development of colorectal tumors and colonic (predominantly adenomatous) polyps at an early age. In addition, MAP is associated with extracolonic manifestations, including duodenal polyposis, and an increased predisposition to ovarian, bladder, skin, and breast cancer. A variety of different benign cutaneous tumors have also been observed in MAP patients, such as sebaceous gland adenomas and epitheliomas, and subcutaneous lipomas [4–6].

MAP phenotype can partially overlap familial adenomatous polyposis (classical FAP), attenuated FAP (AFAP), and, more rarely, Lynch syndrome (LS) [7–14]. When compared to classical FAP patients, MAP patients tend to develop fewer adenomas at a later age: most are diagnosed with colorectal adenomas during the fifth decade of life and about half of them also have colorectal cancer at the time of syndromic diagnosis [7, 8, 15–17]. A more discrete phenotype with a smaller number of adenomas or colorectal cancer without polyposis (fewer than 10 adenomas) has also been described in *MUTYH* mutation carriers under the age of 60 years [18–20]. Usually, biallelic MUTYH mutation carriers have 10–99 adenomas, and less frequently, they develop more than 100 adenomas (only two biallelic *MUTYH* mutation carriers with more than 500 polyps have been reported so far) [17]. Among FAP or AFAP patients without identifiable germline adenomatous polyposis coli (APC) mutations, biallelic *MUTYH* mutations were found in about 28% and 14% of those with 10–100 and 100–1,000 polyps, respectively. Balaguer et al. (2007) showed that the combination of more than 15 synchronous colorectal adenomas and colorectal cancer (CRC) diagnosed under the age of 50 years correlated with biallelic *MUTYH* mutations with a sensitivity of 75% and a specificity of 94% [21]. Overall, biallelic germline *MUTYH* mutations are estimated to occur in 0.2–0.9% of all colorectal cancer patients [22].

The *MUTYH* gene harbors significant molecular heterogeneity with close to 300 different sequence variants identified so far (*MUTYH* Leiden Open Variation Database; http://www.lovd.nl/MUTYH/). The mutations initially identified by Al-Tassan and colleagues [1] were at highly conserved residues and included two hotspot mutations: p.Y179C in exon 7 and p.G396D in exon 13. The p.Y179 mutation occurs in a helix–hairpin–helix domain which plays an important role in 8-oxoG recognition and of binding with adenine mispair specificity, intercalation into the DNA duplex, and stability of the protein–DNA complex. The other common mutation, p.G396, located in the C-terminal domain, is also involved in 8-oxoG recognition and adenine mispair specificity and is thought to be important for conformational flexibility of the mutyh protein [23–25]. D'Agostino et al. [25] demonstrated that the homozygous p.Y179C mutyh protein was totally inactive, while the DNA-glycosylase activity of the homozygous p.G382D was only slightly affected. Recently, Nielsen et al. showed that the phenotype in p.Y179C homozygotes was more severe than that in p.G396D homozygotes [17]. Together, the two common hotspot mutations account for approximately 80% of all reported mutant alleles in Caucasian MAP patients [26].

Identification of biallelic *MUTYH* mutation carriers is important to direct clinical management decisions, considering that in mutation-positive individuals, colonic surveillance should start at age 18–20 years and gastroduodenal surveillance at age 25–30 years [27]. In addition, identification of a biallelic carrier usually is associated with identification of additional at-risk siblings that may also benefit from increased colonic surveillance.

Considering that there is no data available on *MUTYH* genotypic and allelic frequencies in Brazilian patients with different colorectal cancer syndromes, the aim of this study was to assess, in an exploratory approach, the frequency of the two hotspot *MUTYH* mutations (p.Y179C and p.G382D) in Brazilian patients with clinical phenotypes MAP, FAP, Lynch syndrome, and sporadic colorectal cancer (SCRC).

Materials and methods

Patients

The study population (n=75) consisted of four subgroups, including patients with clinical diagnoses of: (a) MAP syndrome (15 patients with 10–99 adenomatous polyps in the colorectum with or without CRC and a pedigree suggestive of recessive inheritance); (b) familial adenomatous polyposis (15 patients with >100 colonic polyps and with or without CRC and other extracolonic features); (c) Lynch syndrome, 15 CRC patients fulfilling Amsterdam (LS-Am) and 15 CRC patients fulfilling Bethesda (LS-Bet) criteria; and (d) SCRC, 15 patients with CRC diagnosed at age 60 years or older without family history of CRC. Patients were consecutively recruited from the cancer-risk evaluation and coloproctology clinics during a period of 18 months (2008–2009). Patients were not classified by ethnicity. One of the most interesting features of the Brazilian population is its heterogeneity. Apart from native populations (Amerindians), Brazil has received immigrants from different countries, including an important contribution from Southern European colonizers (mainly Portuguese and Spanish in the 16th century), Africans (late 17th century), and Northern Europeans (19th century). The influx of immigrants from very diverse geographical and ethnic backgrounds contributed to the formation of the contemporary Brazilian genetic pool, and this high degree of admixture can be observed in the entire Brazilian territory [28]. Phenotype correlates poorly with ancestry as determined by molecular markers, and, as a consequence, the precise ethnic background of an individual seen in routine clinical practice is difficult to determine. The southernmost region of Brazil (the geographic area of this study) is characterized by a trihybrid population that has received native American, African, and especially European ancestors.

The study was approved by the institutional ethics committee, and informed consent was obtained from all participants before recruitment. Clinical data of each patient were reviewed by at least two independent investigators, including colonoscopy, pathology, and surgical records. Family history and criteria for hereditary CRC syndromes were reviewed by at least two clinical geneticists, independently.

Screening for *MUTYH* mutations

Genomic DNA was extracted from peripheral blood using the Ilustra™ blood genomicPrep Mini spin Kit (GE Healthcare) as described by the manufacturer, and DNA concentration and purity were assessed with a NanoDrop ND-1000 spectrophotometer (New England Biolabs). Samples were screened for *MUTYH* mutations p.Y179C (Assay-by design) and p.G396D (assay c_27860252_10) by allelic discrimination with allele-specific TaqMan® probes (Applied Biosystems). Samples were run on an MX 3000P™ qPCR System-Stratagene (Agilent Technologies Inc., Sta. Clara, CA, USA), and allelic discrimination was performed using the Stratagene MxPro QPCR Software. To confirm *MUTYH* mutations detected by TaqMan assay, all mutation-positive samples were submitted to bidirectional gene sequencing (heterozygotes: entire coding region, exons 1–16 and flanking exon–intron boundaries; homozygotes: exon of interest) on an ABI PRISM 3130XL Genetic Analyzer (Applied Biosystems by Life Technologies, Carlsbad, CA, USA) as described previously by Aretz 2006 [29].

Results

Clinical and demographic data of patients included in the study are summarized in Table 1. CRC was present in the majority of patients, and, as expected, the age at CRC diagnosis was significantly different in patients with hereditary vs. those with sporadic phenotypes. In addition, most of the patients had a diagnosis of colonic polyps upon colonoscopy. A significant proportion of patients with confirmed colonic polyps (28/44, 63.8%) had 10–99 colonic polyps, a phenotype consistent either with AFAP, Lynch syndrome (Bethesda criteria), or MAP syndrome. Mucinous CRC was a reported feature of 10% (6/60) of the tumors.

The common germline *MUTYH* mutations, p.Y179C and p.G396D, were detected in homozygosity (two cases) or heterozygosity (three cases) and in the latter group, either with a WT counterpart allele or as compound heterozygotes with other less frequently described mutations (Table 2). Presence of at least one common mutant allele was observed in 5 (10.6%) out of 47 patients with colonic polyps. Overall, biallelic *MUTYH* mutations were identified in 4 (8.9%) of 30 patients with either FAP or MAP criteria, being three of these MAP families. An overlap of phenotypes was observed in some families and two of the mutation-positive MAP families also fulfilled Bethesda criteria. Detailed phenotypic/genotypic characteristics and family histories of the five *MUTYH*-mutation carriers are described in Table 2 and depicted in Fig. 1, respectively.

Discussion

Mutations causing MAP are distributed across the *MUTYH* locus, and various population-specific mutations have been

Table 1 Clinical description of the sample studied (n=75)

	n	Percentage (%)	Mean	SD
Sex				
Female	45	60		
Age at diagnosis of the first tumor (years)			50.4	25.4–33.6
Inclusion criteria				
MAP	15	20		
FAP	15	20		
Lynch–Amsterdam II	15	20		
Lynch–Bethesda	15	20		
Sporadic	15	20		
Reported consanguinity (families)	2	2.7		
Site of tumor (in proband)				
Colon and rectum	60			
Endometrium/ovary	3			
Presence of polyps (proband)	47	62.7		
Number of colonic polyps in probands (n=44)				
<10 polyps	21	47.7		
10–99 polyps	7	15.9		
100–500 polyps	3	6.8		
>500 polyps	2	4.5		
Undetermined $n°$ of polyps	11	25		

Three patients with Amsterdam criteria were diagnosed with endometrial/ovarian cancer

SD standard deviation, *CRC* colorectal cancer

reported. The presence of *MUTYH* germline mutations has been described in approximately 28% of individuals with the "oligopolyposis phenotype" (10–99 polyps) and 7–22% of those with the classical form of FAP [16, 27, 29–31]. It is also known that MAP patients can show a phenotypic overlap with patients fulfilling Bethesda criteria for Lynch syndrome depending on family size and tumor characteristics [9, 13, 27, 32]. In our study we also identified this overlap in some patients, with 5/15 MAP patients fulfilling Bethesda criteria and two of Bethesda patients fulfilling also MAP criteria.

Overall, we identified at least one allele carrying a *MUTYH* germline mutations in five patients of the entire case series. No mutation was identified in either the Lynch syndrome Amsterdam criteria group or the SCRC group. Among the five mutation-positive individuals, two identified as "case 4" and "case 5" (Table 2) met clinical criteria for FAP syndrome. The more severe phenotype with over 100 polyps observed in case 4 (p.Y179C homozygote) is consistent with recent clinical and functional studies published in the literature [1, 21, 33, 34]. Case 5, a patient that also had classical FAP phenotype, was found to be heterozygous for a common *MUTYH* mutation, and bidirectional sequencing of the entire *MUTYH* coding region failed to identify another sequence variant. The personal and family history is typical for classical FAP in this case: four generations are affected by CRC and most of the affected individuals have hundreds of polyps. Although there has been some evidence suggesting that heterozygous mutations in *MUTYH*

Table 2 Detailed description of clinical phenotype of the five *MUTYH* germline mutation carriers

Case	Sex	Criteria	CRC dx (years)	MUTYH genotype	Number of polyps	Polyp description	Polyp location	CRC location	CRC histology
1	M	MAP LS-Bet	45	p.G396D/p.G396D	7	Tubulous and tubulovillous	Rectum and sigmoid	Rectum	Adenoca
2	F	MAP	52	p.G396D/p.Asp16His	56	Tubulous	Multiple sites	Rectum	Adenoca
3	F	MAP LS-Bet	–	p.Y179C/c.1145delC	10	Tubulovillous	Multiple sites	–	–
4	F	FAP	58	p.Y179C/p.Y179C	>100	Tubulous and tubulovillous	Rectum and sigmoid	Sigmoid	Adenoca
5	F	FAP	26	p.G396D/WT	150	Tubulovillous	Multiple sites	Rectum	Adenoca

CRC dx age at diagnosis of colorectal cancer, *M* male, *F* female, *Adenoca* adenocarcinoma

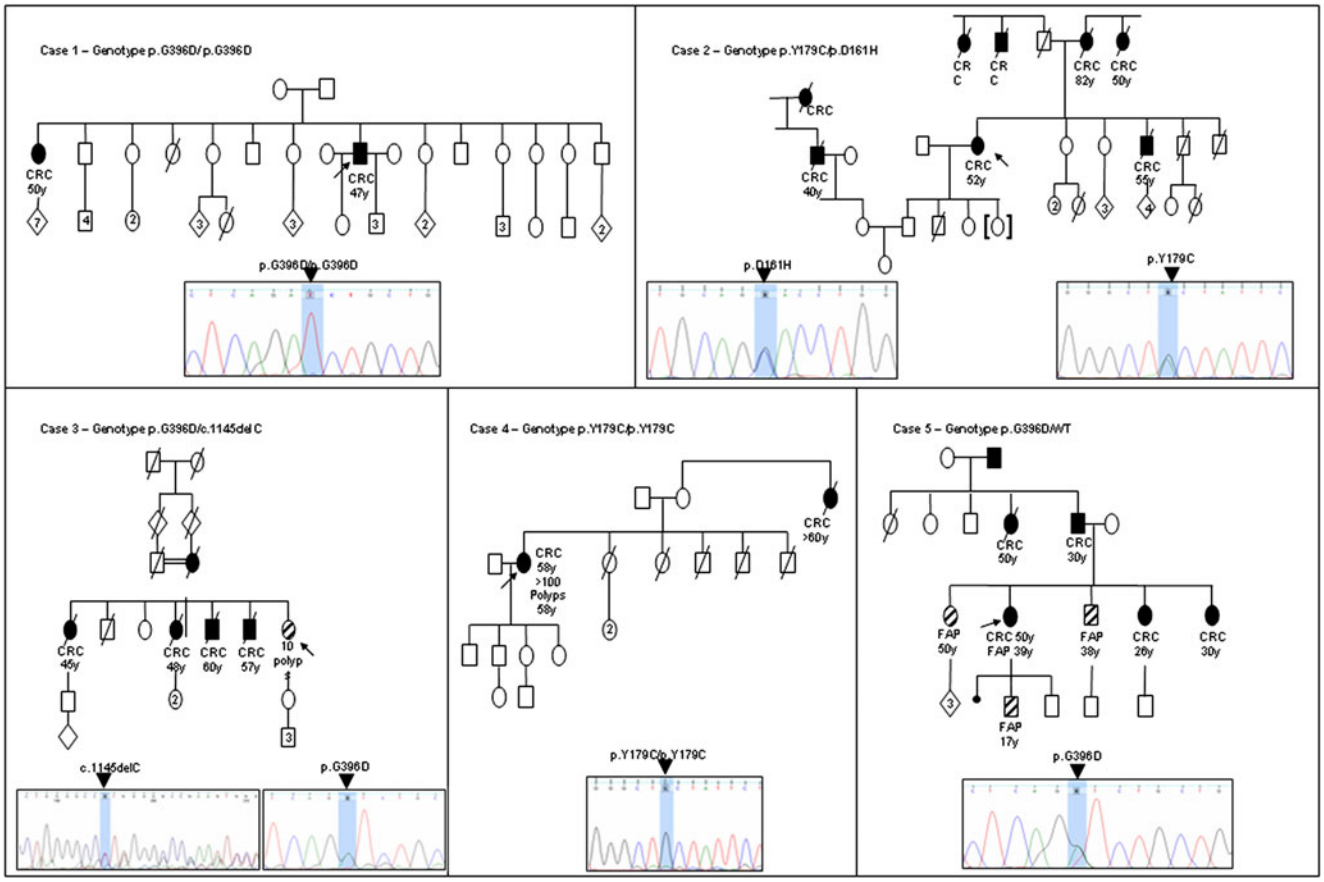

Fig. 1 Pedigrees and sequencing electropherograms of the five patients with germline mutations in *MUTYH* gene. The proband is indicated by and *arrowhead*. *Solid symbols* indicate cancer-affected individuals. *Lined symbols* indicate multiple polyps. *CRC* colorectal cancer, *y* years, *double lines* indicate consanguinity

may be associated with an increased risk for CRC at later ages and mild polyposis, this genotype has not been associated with the full-blown FAP phenotype, and thus, APC mutation testing must be performed to further investigate this particular case. Consanguinity, a clinical feature that is strongly suggestive of MAP in families with a recessive inheritance pattern of polyposis and CRC, was reported by only 2 of the 60 probands with evidence of hereditary colorectal cancer. The differences observed on certain phenotypic features between our series and others described in the literature may be due to our relatively small number of MAP families or may be related to phenotypic peculiarities in this specific population.

In this report, screening of Brazilian patients with colorectal cancer for the common germline *MUTYH* mutations p.G396D e p.Y179C followed by bidirectional sequencing of the heterozygotes was able to identify biallelic gene mutations in 4/60 (6.6%) of individuals with a hereditary CRC cancer phenotype (all syndromes included), 4/30 (13.3%) of individuals with the MAP or FAP phenotype. Slightly higher mutation detection rates (20%) were observed with this approach in the subgroup of patients with the MAP phenotype. In several mutation-positive individuals, there was an overlap of clinical criteria, especially between MAP phenotype and Bethesda criteria. These findings reinforce the importance of considering *MUTYH* mutation screening not only in patients fulfilling MAP criteria but also in those with other hereditary CRC phenotypes, in particular those with associated colonic polyposis.

Additional mutation screening studies of the *MUTYH* gene and analysis of the entire coding region of the gene in a larger number of CRC cases in Brazil will be necessary to confirm these results and determine the sensitivity and specificity of *MUTYH* mutation screening in the differential diagnosis of hereditary colorectal cancer in this admixed population

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