MUTYH-Associated Polyposis: The Irish Experience

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Abstract

MUTYH is involved in DNA damage repair. Bi-allelic MUTYH mutations predispose to polyposis and gastrointestinal malignancies, distinct genetically from autosomal dominant familial adenomatous polyposis coli. Two common European MUTYH mutations account for 90% of MUTYH-associated polyposis (MAP). We aimed to examine the incidence of MAP in Ireland. A retrospective cohort study was undertaken. Patients undergoing MUTYH testing from 2003-2016 were identified by searching electronic databases using terms "MUTYH" and "MYH". Phenotypic and genotypic details were obtained by chart review. Bi-allelic mutations were confirmed in 26 individuals (17 families), of whom 16 (62%) developed colorectal malignancies, and 22(85%) polyposis. Eleven families had bi-allelic status for one/both common European mutations. Regional variation was noted, with over-representation of bi-allelic mutation carriers in the South-west of Ireland. MAP is under-diagnosed in Ireland. Increased awareness is required to facilitate appropriate identification and surveillance of bi-allelic mutation carriers for colorectal pathology.

Introduction

To date, numerous colorectal cancer and polyposis syndromes have been described, including familial adenomatous polyposis (FAP), Peutz-Jeghers syndrome, Juvenile polyposis syndrome and hereditary mixed polyposis. Polyposis syndromes confer a risk of malignancy as well as polyps, given that, irrespective of the genetic aetiology, changes in any individual polyp along the adenoma-carcinoma pathway may lead to the development of colorectal cancer, a risk that increases with increasing polyp burden. Lynch syndrome (Hereditary Non-Polyposis Colorectal Cancer syndrome) predisposes to colorectal and other cancers in the absence of preceding polyposis[1].

MUTYH-associated polyposis (MAP) was the first recessively-inherited polyposis syndrome to be described[2]. The phenotype of MAP is similar to that of attenuated familial adenomatous polyposis (FAP), with colonic polyp burden ranging from tens to a few hundred, developing at a mean age of fifty. MAP is also associated with other

gastrointestinal polyps, duodenal cancer[3] and extra-intestinal malignancies, including ovary and bladder. There is also some conflicting evidence of an association with breast and endometrial cancers [3-5].

To date, 306 unique DNA variants in *MUTYH* have been detected in 8514 individuals worldwide[6]. In Northern European populations however, bi-allelic combinations of two common missense variants, c.536A>G (p.Tyr179Cys) in exon 7 and c.1187G>A(p.Gly396Asp) in exon 13, are reported in 70% of patients with MAP[7], and at least one of these two mutations are detected in 90% cases. The combined carrier frequency of the two common mutations in unaffected controls of European origin ranges from 1 in 80 to 1 in 500[7]. Large ethnic variations in carrier frequency exist, however, and the two common missense mutations have not been reported with the same frequency in Asian [8, 9] or Jewish populations [10], suggesting a founder effect [7].

The majority of germline testing of *MUTYH* for patients in the Republic of Ireland is co-ordinated through a single molecular laboratory based in the Department of Clinical Genetics at Our Lady's Children's Hospital Crumlin. The aims of this study were to examine the incidence and impact of MYH mutations in Irish patients referred for genetic counselling/testing, to identify a genotype-phenotype association, and to investigate the clinical outcome of mono-allelic *MUTYH* mutation carriers.

Methods

A retrospective cohort study was undertaken. The cohort under investigation included mono-allelic and bi-allelic *MUTYH* carriers identified on testing performed via the molecular laboratory in Our Lady's Children's Hospital Crumlin. Probands included Irish patients tested in Ireland; patients of non-Irish origin tested in Ireland, and Irish patients tested abroad where family members had attended for cascade testing. Patients referred for *MUTYH* testing between 2003 and February 2016 were identified by searching departmental electronic patient databases (*iGene* and *Crumbase*) using keywords "*MUTYH*" and "*MYH*". Mutation testing was performed by real-time assay for two common European mutations, with full sequencing of the gene in the case of patients with convincing MAP phenotype with only mono-allelic or no mutation detected by rtPCR. Six probands with severe phenotype also underwent sequencing of the APC gene. Details regarding phenotype and genotype were obtained by chart review.

Results

MUTYH analysis was performed in 120 patients from 61 families, including diagnostic testing in 58 probands. Seventeen unrelated probands were found to carry bi-allelic *MUTYH* mutations, including one patient of Portuguese ethnicity. One proband with a convincing phenotype underwent diagnostic testing for the two common European

mutations only. One mutation has been identified, and full *MUTYH* sequencing is underway to identify the second mutation. During cascade screening, a further nine bi-allelic mutation carriers and twenty-nine mono-allelic mutation carriers were identified (Table 1).

Table 1: Genotypic Frequency

	Genotype of Proband: DNA change	***Protein Change:***	***Diagnostic Tests (n)***	***Cascade Tests (n)***
Bi-allelic mutation carriers	c.1187G>A/c.1187G>A	(G396D/G396D)	3	3
	c.1187G>A/c.1435G>T	(G396D/V479F)	1	1
	c.1187G>A/c.933+3A>C	(G396D/G264Wfs*7)	1	2
	c.536A>G/ c.1187G>A	(Y179C/G396D)	3	0
	c.536A>G/ c.1147delC	(Y179C/A385Pfs*23)	2	0
	c.536A>G/c.1227_1228dupGG	(Y179C/E410Gfs*43)	1	0
	c.536A>G/c.337T>C	(Y179C/W113R)	1	1
	c.536A>G/c.536A>G	(Y179C/Y179C)	4	2
	c.933+3A>C/c.933+3A>C	(G264Wfs*7/ G264Wfs*7)	1	0
	c.1187G>A/pending	(G396D/?)	1	0
	Total		19	9
Mono-allelic Mutation Carriers	c.1187G>A	(G396D)	2	14
	c.536A>G	(Y179C)	0	12
	c.933+3A>C	(G264Wfs*7)	0	2
	c.337T>C	(W113R)	0	1
	Total		**2**	**29**

The mutations most commonly reported in our cohort were the two common European mutations, with c.536A>G homozygosity reported in four families; c.1187G>A homozygosity in three families; and compound heterozygosity of the two mutations in three families. Five families had compound heterozygote genotypes including at least one of the two common European mutations. All six bi-allelic c.536A>G homozygous mutation carriers were affected by cancer on a background of polyposis, at mean age 49 years (±13.2). Of six c.1187G>A homozygous mutation carriers, three siblings developed colon cancer at mean age 47.5 years (±6.4). The phenotypes of all bi-allelic mutation carriers are outlined in table 2. There were no cases of duodenal, ovarian, bladder, breast or endometrial cancers among bi- allelic mutation carriers in this series.

Table 2: Bi-allelic Mutation carriers: Phenotype

Genotype	*Patient*	*Cancer*	*Age at diagnosis*	*Polyposis*	*Polyp Burden*
c.536A>G/c.1187G>A	1	Colon	43	Yes	9
	2	-		Yes	10 to 20
	3	-		Yes	
c.536A>G/c.536A>G	4	Colon	67	Yes	
	5	Colon	42	Yes	
	6	Colon	40	Yes	"10s"
	7	Synchronous Caecal and Sigmoid	59	Yes	50
	8	Colon	37	Yes	20
	9	Rectum		Yes	
c.536A>G/c.337T>C	10	Rectum	36	Yes	
	11	-		Yes	"multiple"
c.536A>G/ c.1147delC	12	-		Yes	55
	13	Rectum	39	Yes	"multiple"
c.536A>G/c.1227_1228dupGG	14	Colon	35	Yes	30
c.1187G>A/c.1435G>T	15			Yes	
	16			Yes	60
c.1187G>A/c.933+3A>C	17	Colon	56	Yes	
	18			Yes	
	19	Colon			
c.1187G>A/ c.1187G>A	20	Colon	52		
	21	Colon			
	22	Colon	43		
	23			Yes	1
	24			Yes	
	25			Yes	
c.933+3A>C/ c.933+3A>C	26	Colon	47	Yes	112
c.1187G>A/second mutation pending	27			Yes	Extensive

Two patients were found to carry variants of unknown significance after undergoing full MUTYH sequencing. One of these patients had ~12 polyps at age 49, and was found to carry two variants of uncertain significance, c.-2C>G (p.Ala2Pro) and c.1256C>A (p.Ala419Asp). Another patient presented with polyposis at age 79, and was found to carry a single MUTYH variant c.312C>T (p.Tyr104=).

Table 3: Mono-allelic Mutation carriers: Phenotype

MUTYH Mutation status	***Testing***	***Genotype***	***Phenotype***
Confirmed	Diagnostic (NGS panel)	c.1187G>A/c.1187G>A	Pancreatic Adenocarcinoma
Confirmed	Diagnostic (NGS panel)	1. *MUTYH*: c.1187G>A 2. *APC*: c.568delG	Polyposis
Obligate carrier	Untested	c.536A>G	Polyposis (5 polyps at 36)
Obligate carrier	Untested	c.1187G>A	Stomach cancer
Obligate carrier	Untested	c.1187G>A OR c.536 A>G	Stomach cancer
Obligate carrier	Untested	c.536 A>G	Oesophageal cancer
Obligate carrier	Untested	c.536 A>G	Endometrial cancer (Microsatellite stable)
Obligate carrier	Untested	c.933+3 A>C	Colorectal cancer
Obligate carrier	Untested	c.1187G>A OR c.1435G>T	Colorectal cancer
Confirmed	Pre-symptomatic	c.933+3 A>C	hyperplastic gastric polyps
Confirmed	Pre-symptomatic	c.536A>G	Single colonic polyp at 40

Diagnostic testing of patients for cancer predisposition using next-generation panels including MUTYH identified a number of mono-allelic mutation carriers. One patient underwent such testing following diagnosis of adenocarcinoma of the pancreas on a background of strong familial history of colorectal, ovarian, liver and pancreatic cancer. In this family, the *MUTYH* mutation was not shown to segregate with disease. Another index patient underwent panel testing for polyposis predisposition, and was found to carry a single paternally inherited *MUTYH* mutation (c.1187G>A) as well as a pathogenic de novo mutation in the *APC* gene (c.568delG, p.Glu190Asnfs*15). This patient had a classical phenotype of Familial Adenomatous Polyposis, with 250 adenomatous polyps on colonoscopy aged 21 years. There was no family history of polyposis or cancer in this instance. Several obligate carriers of MUTYH mutations were noted to have a previous history of malignancy, including of the stomach, oesophagus and endometrium as well as colorectal disease (Table 3). However the majority of obligate carriers did not report a history of malignancy or polyposis. Among mono-allelic MUTYH mutation carriers picked up on cascade testing (n=29), the majority had not undergone colonoscopy. Of those that did (n=8), seven had normal tests, and one had a solitary colonic polyp.

Table 4: County/Country of Origin

Family	*County/Country of Origin*	*Genotype of Proband: DNA change*	*Protein Change:*
1	Cork	c.536A>G/c.1187G>A	(Y179C/G396D)
2	Cork	c.536A>G/c.536A>G	(Y179C/Y179C)
3	Cork	c.536A>G/c.536A>G	(Y179C/Y179C)
4	Cork	c.536A>G/c.536A>G	(Y179C/Y179C)
5	Cork	c.536A>G/ c.1147delC	(Y179C/A385Pfs*23)
6	Cork	c.1187G>A/ c.1187G>A	(G396D/G396D)
7	Dublin	c.1187G>A/c.933+3A>C	(G396D/G264Wfs*7)
8	Dublin	c.1187G>A/ c.1187G>A	(G396D/G396D)
9	Dublin	c.536A>G/c.1187G>A	(Y179C/G396D)
10	Kerry	c.536A>G/c.1187G>A	(Y179C/G396D)
11	Kerry	c.536A>G/ c.1147delC	(Y179C/A385Pfs*23)
12	Kerry	c.1187G>A/ c.1187G>A	(G396D/G396D)
13	Waterford	c.536A>G/c.536A>G	(Y179C/Y179C)
14	Galway	c.536A>G/c.337T>C	(Y179C/W113R)
15	Galway	c.1187G>A/c.1435G>T	(G396D/V479F)
16	Limerick	c.933+3A>C/c.933+3A>C	(G264Wfs*7/ G264Wfs*7)
17	Portugal	c.536A>G/c.1227_1228dupGG	(Y179C/E410Gfs*43)
18	Louth	c.1187G>A/mutation pending	G396D/second mutation pendir

A local geographical difference in incidence of *MUTYH*-associated polyposis was noted, with marked predominance in the South of the country (table 4). Six of sixteen apparently unrelated families originated from Co. Cork, a further three from neighbouring Co. Kerry, and one from Co. Waterford. Another family originated in Co. Limerick, and two from Co. Galway. A disproportionately small number of families (n=3) originated from Co. Dublin, given the distribution of the population in Ireland. One family was of Portuguese origin and now live in Dublin. The rates of colorectal cancer nationally have also shown a regional variation, with observed incidence of colorectal cancers. Invasive cancers in Co. Cork have been higher than that expected in both periods between 1994-2003 and 2004-2012 [11].

Discussion

Cancer arises as a result of sequential acquisition of genetic mutations, caused by exogenous or endogenous mutagens. There are intrinsic DNA repair mechanisms to repair such mutations, and MYH polyposis is a genetic disorder of one such DNA repair mechanism. DNA repair mechanisms have generated particular interest of late, given that last year's Nobel Prize in Chemistry was jointly awarded to three renowned scientists in this field[12].

In our series, c.536A>G homozygotes were found to develop a more severe phenotype than c.1187G>A homozygotes or c.536A>G/c.1187G>A compound heterozygotes. All c.536A>G homozygotes developed polyposis and subsequent colorectal malignancy. Comparatively, the cancers occurring in c.1187G>A homozygotes were limited to a single sibship (n=3), with one further c.1187G>A homozygote in the same family developing only a single benign

polyp. One of three c.1187G>A/c.536A>G compound heterozygote developed early onset colon cancer. This finding has been previously documented[7,13] and is attributed to different effects of these mutations at a functional level. The c.1187G>A mutation acts to structurally modify a C-terminal turn, resulting in partially deficient DNA glycosylase activity, and appears to be less catalytically compromised than the c.536A>G mutation in the N-terminal catalytic base excision domain which results in dramatically reduced glycosylase activity and reduced base-flipping ability[2,7,14]. The c.536A>G mutation is also more often associated with larger accumulation of endogenous DNA damage [14]. Interestingly, in our series, four patients developed malignancy without prior polyposis, of whom three were c.1187G>A homozygotes, and one c.1187G>A/c.933+3A>C compound heterozygote. This is in-keeping with previous literature, highlighting a risk of colorectal cancer in MAP even in the absence of polyposis [15].

Other mutations identified in our cohort included a Portuguese founder mutation, c.1227_1228dupGG (p.Gly410Glyfs) [16] in a Portuguese patient; c.1435G>T (p.Val493Phe), previously reported in a French cohort [17], and c.1147delC (p.Ala385Profs*23), common in patients of Northern European origin [7]; and c.933+3A>C (p.Gly264Trpfs*7), which has been reported as an Italian founder mutation, and with lesser frequency in other Western European populations [17, 18]. A novel c.337T>C (p.Trp113Arg) variant was detected in two compound heterozygotes with convincing MAP phenotypes. In silico analyses suggest high likelihood of pathogenicity.

A single patient in our cohort with a c.933+3A>C homozygous genotype had the most severe polyp burden in the cohort, as well as early onset malignancy, This mutation alters the sequence of the donor splice site in intron 10, resulting in skipping of exon 10 [18]. In lymphoblastoid cell lines (LCLs), this splice-site mutation was found to encode a non-functional protein (G264WfsX7). The amount of normal protein produced by LCLs with c.933+3A>C depends on the second mutation, and ranges between 1-100% of that produced by wild type LCLs. In c.933+3A>C/c.933+3A>C homozygous LCLs some primary transcripts were noted to avoid abnormal splicing, resulting in formation of some full-length, wild-type protein [19]. Homozygous c.933+3A>C/c.933+3A>C cell lines were noted to produce ~10% normal protein [18]. Maintenance of some residual *MUTYH* activity should predict an attenuated phenotype in c.933+3A>c/c.933+3A>C homozygotes compared to carriers of mutations associated with complete *MUTYH* inactivation [18]. The severe phenotype in the patient with this genotype in our cohort is therefore suggestive of a possible concomitant genetic or environmental modifier.

The risk of colorectal cancer in heterozygous carriers of a single *MUTYH* mutation is unclear. A large scale meta-analysis suggests that there may be a marginally risk associated with mono-allelic c.536A>G mutations, but not for c.1187G>A, but this effect did not retain statistical significance after Bonferroni correction for multiple analyses [13], and was not felt to be clinically actionable. In this series, no mono-allelic carriers picked up on cascade testing

had a history of malignancy or polyposis, and colonoscopic screening undertaken by some of these patients (n=8) revealed a solitary polyp in only one individual. Considering only parents of bi-allelic carriers, this series includes at least 34 obligate carriers, and most did not have a positive history of malignant disease, although cancers were reported in 6 individuals.

Given the phenotype associated with bi-allelic *MUTYH* mutations, it is strongly recommended that bi-allelic mutation carriers be appropriately identified to facilitate surveillance for colorectal disease. For full siblings of patients with MAP, assuming the parents are obligate carriers, the risk that they are also affected is 1 in 4 (25%), while the risk that they are a mono-allelic carrier is 2/3 (66%). The risk of transmission of a single mutation in *MUTYH* to the child of a bi-allelic mutation carrier is 100%, but the risk of the child being affected by MAP (i.e. inheriting second mutation from the other parent) depends on the carrier status of the other parent, who has a general population risk (~1%). Cascade testing in our centre is offered to sibs, partners and/or offspring of bi-allelic mutation carriers. Current screening guidelines for mono- and bi-allelic *MUTYH* mutation carriers are based on recommendations following from a meeting of European experts in Mallorca in 2007 [20]. Currently, colorectal surveillance of bi-allelic *MUTYH* mutation carriers follows that of patients with *APC*-related familial adenomatous polyposis, with colonoscopy recommended to start between 18-20 years, at 2-yearly intervals. Screening of mono-allelic *MUTYH*-carriers is not recommended outside of national screening programs [20].

The prevalence of bi-allelic *MUTYH* mutations is expected to be between 1/40,000-1/20,000[21]. Given a population of ~4.8 million in Ireland, we can estimate that there are 120-240 bi-allelic mutation carriers in the country. A minority of these will be children or young adults who have not yet developed symptoms of the condition. It is clear however, that *MUTYH*-associated polyposis is under-recognised and under-diagnosed in Ireland. *MUTYH*-gene analysis should therefore be routinely considered in all patients with polyposis if *APC*-gene analysis is negative or family history suggests recessive inheritance.

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Conflict of Interest

The authors confirm there is no conflict of interest

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