

Genomics of Hereditary Colorectal Cancer: Lessons Learnt from 25 Years of the Singapore Polyposis Registry

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Abstract

Introduction: The Singapore Polyposis Registry (SPR) was established in 1989 in Singapore General Hospital (SGH). The aims were to provide a central registry service to facilitate identification, surveillance and management of families and individuals at high risk of colorectal cancer. **Materials and Methods:** This is a review of published literature in the department. **Results:** The registry currently has 253 families with several genetic conditions—93 familial adenomatous polyposis (FAP) families, 138 Amsterdam-criteria positive presumed Lynch syndrome (LS) families, 12 families with Peutz-Jeghers syndrome, 2 families with Cowden's syndrome, and 8 families with hereditary mixed polyposis syndrome (HMPS). There are also 169 families with a strong family history of colorectal cancer but no abnormal genes yet identified. In FAP, a diagnostic tool developed has allowed a 94% local APC germline detection rate in FAP families. Knowledge obtained studying the phenotype of FAP patients has allowed better choice of surgery between ileal pouch anal anastomosis (IPAA) against an ileal-rectal anastomosis (IRA). In LS, our review has noted a highly heterogeneous mutational spectrum and novel variants made up 46.7% (28/60) of all variants identified in this cohort. This may suggest that our Southeast Asian ethnic groups have distinct mutational variants from Western populations. Pathogenic mutations were only confined to *MLH1* and *MSH2*, and identified in 28.8% of families. **Conclusion:** The impact of predictive gene testing for hereditary cancer risk in clinical practice has allowed evolution of care. Risk-reducing surgery and aggressive surveillance allows reduction in morbidity and mortality of patients. The SPR will continue to grow and improve outcomes in hereditary colorectal cancer patients and families.

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Introduction

The significant advancements of genomic information for colorectal cancer (CRC) have been made largely in the last quarter of the century. The loss of the long arm of chromosome 5 in a patient with familial adenomatous polyposis (FAP) was defined in 1986.¹ Significantly, the location was confirmed and refined to 5q22 via linkage studies² and the APC gene was identified as the causative mutation in 1991.³

Up until 1962, FAP was the only known hereditary form of CRC. Henry Lynch's landmark pioneered research work in the now famous Family G, however, identified a different type of hereditary cancer,⁴ which also highlighted the importance of detailed family histories and pedigree

construction. The discovery of mismatch repair (MMR) genes (*MSH2*, *MLH1*, *MSH6*, *PMS2*)⁵ in 1993 enabled identification of mutation carriers and provided certainty that a specific hereditary cancer syndrome other than FAP existed. The roles of microsatellite instability (MSI) and immunohistochemistry (IHC) have also gradually been proven to be of significant aid in the screening and diagnosis of Lynch syndrome (LS).⁶

Hereditary colorectal cancer syndromes are now known to consist of 10% of all colorectal cancers. However, there remains a large proportion (>20%) with a familial predilection for CRC with a syndrome yet to be defined or a genotypic abnormality identified.⁷ The importance of centralising a database, to facilitate identification,

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surveillance and management of families and individuals at high risk of getting CRC has never been more important. The first polyposis registry, the St Mark's Hospital Polyposis Register, was conceived by JP Lockhart-Mummery and C Dukes in 1924.⁸ Since then, many national and regional registries have been set up with considerable impact on the reduction of colorectal cancer in FAP. These include registries in Europe⁹⁻¹¹ as well as Asia,^{12,13} and number more than 50 worldwide. There is increasing evidence that patients with FAP cared for in a registry have lower chance of having CRC at the time of diagnosis, and higher life expectancy than those who are not.^{9,14}

The Singapore Polyposis Registry (SPR) was established in 1989 in Singapore General Hospital.¹⁵ The aims of this initiative were to provide a central registry service to all doctors in Singapore to facilitate identification, surveillance and management of families and individuals at high risk of getting colorectal cancer. FAP families in Singapore were identified so that at-risk individuals may be offered current screening procedures and prophylactic surgery to prevent the almost certainty of developing colorectal cancer. In addition, family members were identified for genetic testing and counselling services provided. From an initial emphasis on FAP and hereditary non-polyposis colorectal cancer (HNPCC), patients with other polyposis types have also been included. The registry has grown in the last 25 years and currently has 253 families with 4 known genetic conditions -93 FAP families, 138 Amsterdam-criteria positive presumed LS families, 12 families with Peutz-Jeghers syndrome, 2 families with Cowden's syndrome, and 8 families with HMPS. There are also 169 other families with a strong family history of colorectal cancer but no abnormal genes yet identified. Key summary of the important findings of these hereditary colorectal cancers will be discussed.

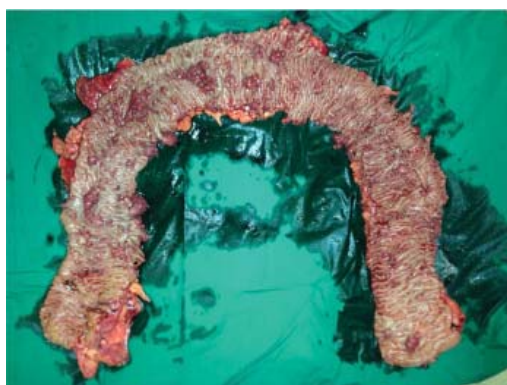


Fig. 1. Endoscopic view of a typical FAP patient.

Familial Adenomatous Polyposis (FAP)

FAP has served as an important model for the understanding of carcinogenesis and the functions of the APC gene and protein have been well studied (Figs. 1 and 2). This tumour suppressor gene codes for a large protein that comprises of 2843 amino acid residues. Severity of the disease and extra-colonic manifestations (ECM) appear to correlate with different sites of mutations. The majority of disease associated germline APC mutations causes protein truncation that enables the protein truncation test (PTT) to be adopted as main technique for mutation detection. In our lab, using a combination of cDNA-PTT, multiplex ligation-dependent probe amplification (MLPA) and differential expression techniques, our local APC germline detection rate in FAP families is 94%.^{16,17} This corroborates favourably against worldwide reported frequencies of 50% to 80% detection.¹⁸ In addition, several novel mutations including large genomic deletions were identified and submitted to the Human Gene Mutation Database (HGMD).¹⁹ These novel mutations have loss of either one or both β -catenin binding sites thus inhibiting its tumour suppressor function of regulating the Wnt/ β -catenin-Tcf signaling pathway.

In our recent clinical review of 122 patients from 88 FAP families, 73% underwent restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) and 21% had total colectomies with ileorectal anastomosis (IRA). The most common ECMs were stomach fundic gland polyps and duodenal adenomatous polyps (29%). This was noted early on in the development of the SPR and was reported in 1992.²⁰ Desmoids were found in 14% of the cases and were located either in the abdominal wall or mesentery. Eight percent had extra-colonic cancers of which thyroid cancers were the most common.²¹

Our reviews of the genotypic and phenotypic

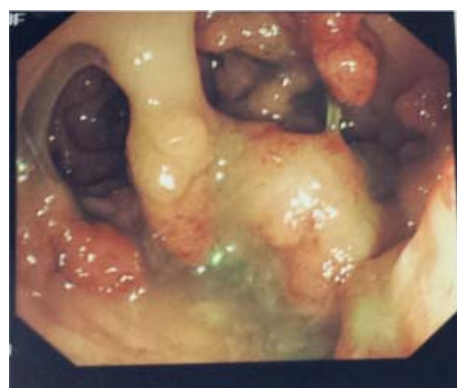


Fig. 2. The same patient who subsequently underwent prophylactic restorative panproctocolectomy and ileal pouch anal anastomosis.

characterisations indicate that Southeast Asian families have some features similar to, and others distinct from Caucasian families from other regions of the world. Fundic gland polyposis and osteomas appeared to be associated with *APC* mutations throughout the coding region and not confined to codon 767-1573 as reported for Caucasian populations. There were also no patients with hepatoblastomas or brain tumours in our local FAP population suggesting that these ECMs are rare in Southeast Asian populations.^{19,21}

In FAP patients with desmoid tumours, we have noted that the clinical progression can be divided into “stable”, “variable”, “progressive” and “aggressive growth” which have implications on follow-up strategies. The majority of desmoids occur approximately 3 years after initial surgery but almost 30% were found to occur before any surgical stimulus. The most common complications to develop were intestinal obstruction, ureteric obstruction and encasement of superior mesenteric vessels. Unfortunately, the clinical course of desmoids remains unpredictable and no significant genetic marker was identified for prognostication.²²

The 10-year overall survival was 75.6% (95% CI, 67 to 84.2%) and the median age of death was 40 years old. Recurrence and disease-free survival was not significantly different for the type of surgery (IPAA vs IRA) performed ($P = 0.486$). This knowledge from the registry allows appropriate decisions to be made on suitable treatment for these young patients. Prophylactic surgery to minimise the risk of developing colon or rectal cancers is required in FAP families but there are various factors to consider. These considerations will be to provide the most appropriate treatment to reduce the risk of developing CRC and yet at the same time to preserve the patients' quality of life at a satisfactory level. This is especially important in FAP patients who have to undergo radical surgery and are often young, with minimal or no symptoms. The choice of surgery remains much debated upon. While IPAA was the most common procedure performed in our department, there was a relatively large number of IRAs performed with no difference in disease-free survival. Restorative proctocolectomy was described to eradicate all at-risk colorectal mucosa and yet maintain the anal canal for good functional outcomes. But complications reported include a higher risk of night-time soilage, sexual and urinary dysfunction as well as a need for temporary defunctioning ileostomy. It may be noted from the review that IRA may be a suitable option in a select group. Patients suitable for IRA include an attenuated FAP form of disease, relatively few rectal polyps (usually recommended <20 polyps) and most importantly are compliant and willing to undergo lifelong endoscopic surveillance annually. The use of genetic testing has been proposed for 1 surgical technique over another. Bulow et al identified patients with genetic

errors in codon 0-200 or above 1500 and proposed IRA over IPAA for these patients with mild genetic mutations²³ but this has not been studied in our unit as yet.

While the study of *APC* molecular genetics is relatively mature, it continues to provide insights with general relevance to cancer biology, for example, an indel leading to splicing defect in exon 9 of *APC* has resulted in very severe rather than attenuated FAP in one recent case documented in the SPR.²⁴ In particular, the genetic profiling of our Southeast Asian populations with FAP remains relatively unknown especially in the rural areas of the region. And as travel costs reduce and healthcare access becomes more readily available, it is likely that the SPR will continue to provide more insights into mutational profiles of FAP patients.

Other Polyposis Syndromes

There are other rarer polyposis syndromes include MYH-associated polyposis, Peutz-Jegher syndrome (PJS), Cowden's syndrome, juvenile polyposis syndrome, hyperplastic polyposis syndrome and hereditary mixed polyposis syndrome (HMPS). Our reported local experience with PJS and HMPS is discussed in more detail here.

PJS is a rare autosomal dominant inherited condition with intestinal hamartomatous polyposis and mucocutaneous melanocytic macules (Fig. 3). Germline mutation of the *STK11* (serine/threonine kinase 11) gene located on chromosome 19p13 has been shown to cause approximately 50% of PJS cases but not all cases have this mutation, raising the possibility of a second gene.²⁵ The SPR reported experience is limited to its first 7 patients and clinical presentations were usually secondary to polyp related complications. These included recurrent episodes of abdominal colic, intestinal obstruction and gastrointestinal bleeding, as well as the need for repeated laparotomies. These patients were also at increased risk of developing both gastrointestinal and extra-intestinal malignancies.²⁶ There were no genotypic or phenotypic differences compared to



Fig. 3. Mucocutaneous melanocytic macules in a Peutz-Jeghers patient.

reported Western literature although our study population is small. Cancer surveillance guideline for these patients has also been suggested based on the experience from the SPR.²⁶

HMPS is characterised by colonic polyps of mixed hyperplastic, adenomatous and juvenile components. HMPS was first described in a large Ashkenazi family, SM96, and the HMPS locus was first mapped to chromosome 6q, then remapped to 15q13 with further clinical data.^{27,28} However, a study of 8 HMPS Chinese families in our local population showed that a *BMPRI1A* gene defect on chromosome 10q23 was the disease-causing mutation in 50% of these families.²⁹ It is thus suggested in our population, that *BMPRI1A* mutation should be first screened for, if patients have large bowel polyps of mixed histology in the absence of upper gastrointestinal abnormalities, and have a family history suggestive of an autosomal dominant inherited condition.

For these polyposis syndromes, the mode of inheritance, clinical manifestations, criteria for diagnosis and screening suggestions are summarised in Table 1.

Hereditary Non-polyposis Colorectal Cancer (HNPCC)/Lynch Syndrome (LS)

LS is the most common autosomal dominantly inherited CRC and defects in the DNA-mismatch repair genes lead to

multiple errors in repetitive DNA sequences (microsatellites) throughout tumours. This genomic instability is the hallmark of LS tumours and is known as microsatellite instability (MSI). MSI itself is not proof of LS as 10% to 20% of sporadic tumours also show some degree of MSI, most commonly due to hypermethylation of *hMLH1* rather than a germline mutation in the MMR genes. The identification of LS individuals is important as it makes it possible to target effective preventative measures and allow surveillance programmes to be implemented in family members.

Clinical criteria has been modified following improved understanding of the disease. The initial Amsterdam I criteria defined in 1991 to facilitate linkage and positional cloning studies³⁰ was highly specific in order to reduce misclassification of families, but suffered from a lower sensitivity. The Amsterdam II criteria in 1999 were widened to include other extra-colonic cancers³¹ (Table 2). At present, the most important clinical criteria used is the updated Bethesda criteria and this version is widely utilised for patients as an indication for selection of families for mutational analysis³² (Table 2). However, because of the varied population-specific gene mutations, clinical phenotypes and clinical outcomes, other countries have developed their own clinical criteria. For Asian populations in particular, gastric cancer is frequently reported in LS families.

Table 1. Summary of Polyposis Syndromes

	Peutz Jegher's Syndrome (PJS)	Hereditary Mixed Polyposis Syndrome (HMPS)
Genetic defect	Mutation in <i>STK 11</i> gene located on chromosome 19p13	Mutation in <i>CRAC1</i> gene located on chromosome 15q13, <i>BMPRI1A</i> on 10q23
Inheritance	Autosomal dominant with variable penetrance	Autosomal dominant with high penetrance
Age of onset	Median of 11 years old	1. First polyp in late 20s 2. Colorectal cancer at 50 to 60 years old
Gastrointestinal manifestations	1. Harmatomatous polyps most frequently involving the small bowel, but can also involve the colorectum and stomach 2. Increased risk of oesophageal, gastric, small intestinal and colonic cancer	3. Colorectal polyps of multiple and mixed morphologies, including serrated lesions, Peutz-Jeghers polyps, juvenile polyps, adenomas and colorectal carcinoma, involving both proximal as well as distal colon 4. Increased risk of colorectal cancer 5. No upper gastrointestinal manifestations
Extra-intestinal manifestations	1. Mucocutaneous hyperpigmentation 2. Increased risk of pancreatic, breast, uterine, ovarian and testicular cancer 3. Harmatomatous polyps in bladder, lungs, nose, uterus and gallbladder	Wilms' tumour and thyroid carcinoma are associated with germline <i>BMPRI1A</i> mutations
Criteria for diagnosis	Histopathologically confirmed hamartomatous polyps and at least 2 of the following clinical criteria: 1. Family history 2. Mucocutaneous hyperpigmentation 3. Small bowel polyposis	No specific criteria. Suspected in individuals and families with a history of multiple polyps of multiple and mixed morphologies, with absence of upper gastrointestinal manifestations
Screening suggestion	Two-yearly surveillance for gastric and small bowel polyposis with upper gastrointestinal endoscopy and small bowel series or capsule endoscopy, beginning at age 10	Two-yearly colonoscopy beginning 5 to 10 years before the age of onset of youngest family member

Table 2. Amsterdam I and II Criteria, and Bethesda Guidelines for Lynch Syndrome

Amsterdam I Criteria - Families Must Fulfill All Criteria	
1.	At least 3 relatives should have histologically verified CRC; 1 of them should be a first-degree relative to the other 2.
2.	At least 2 successive generations should be affected.
3.	In 1 of the relatives, CRC should be diagnosed under 50 years of age.
4.	FAP should be excluded.
Amsterdam II Criteria - Families Must Fulfill All Criteria	
1.	There should be at least 3 relatives with an HNPCC-associated cancer (colorectal, endometrium, stomach, small bowel, ureter or renal pelvis, brain, hepatobiliary tract and skin).
2.	One should be a first-degree relative of the other 2.
3.	At least 3 successive generations should be affected.
4.	At least 1 should be diagnosed before age 50.
5.	FAP should be excluded in the colorectal case(s), if any.
6.	Tumours should be verified by pathological examination.
Bethesda Guidelines for Testing for Colorectal Tumour for Microsatellite Instability	
1.	Colorectal cancer diagnosed in a patient who is less than 50 years of age.
2.	Presence of synchronous or metachronous colorectal or HNPCC-associated tumours.
3.	Colorectal cancer with the MSI-H histology diagnosed in a patient who is less than 60 years of age. (Presence of tumour infiltrating lymphocytes, Crohn disease-like lymphocytic reaction, mucinous/signet-ring differentiation or medullary growth pattern)
4.	Colorectal cancer or HNPCC-associated tumour diagnosed under age 50 years in at least 1 first-degree relative.
5.	Colorectal cancer or HNPCC-associated tumour diagnosed at any age in 2 first-or second-degree relatives.

CRC: Colorectal cancer; FAP: Familial adenomatous polyposis; HNPCC: Hereditary non-polyposis colorectal cancer; MSI-H: Microsatellite instability-high

In LS, there is an estimated 68% to 82% lifetime risk of CRC, early age of onset of related cancers; tumours are predominantly located in the proximal colon (60% to 70%), with approximately 10% to 30% developing synchronous or metachronous cancers. Overall 5-year survival rates in affected family members are better than that seen in sporadic CRC. In our local review of predominantly Chinese patients from 42 families based on Amsterdam I and II criteria, significantly, 69% of tumours in this Amsterdam defined cohort were in contrast left-sided, the majority being sigmoid cancers.³³ This interesting trend in our predominantly Chinese population mirrors a similar review done in China, where a dominant manifestation of left-sided CRCs (60.6%) and lower synchronous tumour incidence (8.5%) was also reported. In this series, only one-third of the kindreds had germline mutations.³⁴ This contrasts with Western reports emphasising the importance of right-sided colon cancer in the diagnosis of LS and has important implications in management of Asian HNPCC patients.

We have recently completed our genetic and epimutational profiling of LS families in Singapore. Amongst the 5 MMR genes screened, pathogenic mutations were only confined to *MLH1* and *MSH2*, and identified in 28.8% of the families.³⁵ The mutational spectrum was highly heterogeneous and novel variants (6 pathogenic, 20 variants of unknown

significance and 2 single nucleotide polymorphisms (SNPs) made up 46.7% (28/60) of all variants identified in this cohort. This again may further reinforce, that our Southeast Asian ethnic groups (Chinese and Malay) have distinct mutational variants from Western populations. Interestingly, 1 recurrent mutation in *MLH1* (c.793C>T) was also observed in 5 patients from 3 unrelated Chinese families, accounting for 21.7% (5/23) of LS cases. This mutation would lead to skipping of exon 10. In Taiwanese Chinese, founder effect of this mutation has been established in 13 LS families.³⁶ While we are not able to confirm the possible founder effect of this mutation in local Chinese LS kindreds, it may potentially be a cost-effective LS screening start point for Singaporean Chinese, before exhaustive scanning of the common MMR genes.

One important finding in our study is the 92.9% sensitivity conferred by IHC that surpassed 64.3% sensitivity by MSI. We also noted that 15.6% of patients with MSS tumours harboured pathogenic mutations and thus may potentially have been excluded from further mutational evaluation for MMR defects.³⁵ Our results may thus provide an initial guide to a diagnostic molecular screening algorithm. The over-reliance of Amsterdam criteria should be taken into consideration and this criteria as well as microsatellite marker panels may not be suitable in Asian populations.

In general, IHC screening is simple, fast and cost-effective with little added facilities required and are thus more cost-effective. One additional advantage is that the mutated MMR gene can be pinpointed through a loss of protein staining. IHC in our population may thus be superior to MSI as a screening tool for deficient MMR.

Future of Singapore Polyposis Registry (SPR) and Genetic Testing

Twenty-five years on, the SPR continues to strive to improve outcomes in hereditary colorectal cancer patients and their family members. The impact of predictive gene testing for hereditary cancer risk in clinical practice has allowed evolution of changes in care. Risk-reducing surgery and aggressive surveillance allows reduction in morbidity and mortality of patients. The decision for genetic testing however is a multistep process that requires several decision points. For the individual, this includes: whether to seek counselling; undergo mutation testing; receipt of test results and finally to accept surveillance protocols or possible prophylactic surgery. The other big decision conundrum will be whether and when to share results with family members. It is important as knowledge evolves that awareness of the various psychological outcomes after genetic testing remain paramount to these test individuals especially after disclosure to mutation carriers. Sharing of information to relatives is also sensitive and efforts will continue to encourage individuals to communicate test results to various family members. Future research will be to address current gaps in knowledge, provide informative strategies for facilitating optimal delivery of clinical services for high-risk populations in the nation, as well as provide greater awareness on a national level.

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