Genetic and clinical aspects of inherited syndromes associated with adenomatous polyposis

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CHAPTER 1

General Introduction

GENERAL INTRODUCTION

Hereditary colorectal cancer (CRC) syndromes account for 5-15% of colorectal cancers. Hereditary CRCs are often divided into two major categories: Hereditary polyposis syndromes and non-polyposis syndromes.

Lynch syndrome, an autosomal dominant non-polyposis syndrome, is the most common form of hereditary CRC, responsible for 3-5% of all CRC cases. It is characterized by high risks of developing colorectal and endometrial cancer as well as cancer of urinary tract, stomach, small intestine and other cancers.[1]

Hereditary polyposis syndromes are a group of syndromes characterized by the development of multiple colorectal polyps and/or histopathologically specific polyps and a high risk of developing colorectal cancer at an early age.[2] Familial adenomatous polyposis (FAP) is the most common polyposis syndrome responsible for 1% of all CRC cases.[3] Other less common polyposis syndromes include: MUTYH-associated polyposis (MAP), Juvenile polyposis syndrome (JPS), Peutz-Jeghers syndrome (PJS), PTEN hamartoma tumor syndrome and Constitutional mismatch-repair deficiency syndrome (CMMRD). More recently, next-generation sequencing has identified novel genetic causes of hereditary polyposis syndromes such as polymerase proofreading-associated polyposis (POLD1- and POLE-associated polyposis) and NTHL1- associated tumor syndrome.[2]

PART I: APC-ASSOCIATED POLYPOSIS/FAMILIAL ADENOMATOUS POLYPOSIS (FAP) & MUTYH-ASSOCIATED POLYPOSIS (MAP)

A. APC-ASSOCIATED POLYPOSIS / FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

APC-associated polyposis is an autosomal dominant cancer predisposition syndrome caused by a germline pathogenic variant in the APC gene. About one third of cases are due to *de novo* germline APC. It is estimated that 20% of the *de novo* cases of FAP have somatic mosaicism.[4,5]

Colonic manifestations of FAP include the development of hundreds to thousands of adenomatous polyps. Approximately 50% of FAP patients develop adenomas by age 15 and 95% by age 35.[6] CRC develops a decade after the appearance of polyps and without intervention, the risk is almost 100% by the

age of 50.[7] Attenuated FAP (AFAP) is observed in 8-10% of cases and is characterized by a milder colonic phenotype with <100 adenomatous polyps developing at a more advanced age.[2] Besides the colonic phenotype, patients present with other manifestations including duodenal adenoma and cancer, desmoid tumor and extraintestinal malignancies.

The discovery of the APC pathogenic variants as the cause of FAP, have enabled the identification of FAP in pre-symptomatic individuals. The implementation of surveillance programs and preventive surgical intervention improved the life-expectance of these patients considerably. Due to colorectal surveillance, a shift was observed in the causes of death with less deaths due to CRC and more deaths due to desmoid tumors and duodenal cancer.[8–10]

Genetics

APC is a tumor suppresser gene located on chromosome 5q21-22. The gene consists of 15 exons which encodes a 2843-amino acid protein.[11,12] The APC protein is a component of the Wnt/β-catenin signaling pathway. APC complexes with glycogen synthase kinase-3 (GSK3) and axin and negatively regulates β-catenin by promoting the phosphorylation and ubiquitination. In APC mutation, accumulated β-catenin interacts with T-cell factor (TCF) transcription factor which leads to transcriptional activation of specific genes involved in proliferation, differentiation, migration, apoptosis, and cell-cycle progression.[13,14]

Genotype phenotype studies

Several studies have reported an association between the location of mutation on the APC gene and the severity of colonic disease reflected by the number of polyps and age of onset.[15,16] Correlations between attenuated FAP (AFAP) and mutations before codon 157, after codon 1595 and in the alternatively spliced region of exon 9 are described. Severe polyposis (>1000 adenomas) is correlated with mutations between codons 1250 and 1464 and mutations in the remainder of the APC gene are responsible for an intermediate colonic phenotype.[15]

In addition, attempts have been made to correlate extracolonic features with the site of APC mutation. An association between congenital hypertrophy of the retinal pigment epithelium (CHRPE) and desmoid tumors was observed with mutations between codons 311 and 1444 and after codon 1444, respectively.[15]

Modifier genes in FAP

Phenotypic variability within FAP families with the same APC mutation suggests that besides genotype, other factors play a role in severity of polyposis and risk of CRC. Several modifier genes have been investigated and some genes were found to influence disease severity in FAP.[17–20]

The phenotypic variability among different inbred strains of the Apc (Min) mouse model also highlights the importance of modifier alleles in FAP and several modifiers of Min (Mom) loci associated with the Apc (Min) mutation have been identified to date.[21–23] These modifiers such as Mom1 (modifier of Min 1) and Mom5 which alter tumor phenotypes have also been studied extensively.[24–26]

In the general population, environmental and genetic factors influence risk of CRC.[27] In addition, several single nucleotide polymorphisms (SNPs) identified by genome-wide association studies (GWAS) show an association with sporadic CRC.[28] **Chapter 2** describes a research project that studies the influence of CRC-associated SNPs on disease phenotype in patients with a germline pathogenic variant in APC.

Extracolonic manifestations

Besides colorectal polyposis, many extracolonic manifestations, including benign and malignant features, are observed in FAP patients. Benign extracolonic manifestations include congenital hypertrophy of retinal pigment epithelium (CHRPE), fundic gland polyps, epidermal cysts, dental anomalies and adrenal masses. Duodenal adenoma is found in 80-90% of patients and the risk of duodenal cancer is 5-15%. Other less frequently observed extracolonic neoplasms include cancers of thyroid, brain, stomach, pancreas, liver and desmoid tumors.[20,29]

Substantial decrease in mortality due to CRC has increased the life expectancy of FAP patients. As a consequence, more patients die from other causes including extra-colonic cancers. [6,30,31] The risk of extracolonic cancers such as thyroid, liver and pancreatic cancer in FAP reported in the literature varies widely which led to different opinions regarding the need of surveillance. In **chapter 3**, the occurrence of extracolonic malignancies and the causes of death in a large series of adenomatous polyposis coli (APC) mutation carriers is evaluated and the option of additional surveillance for these cancers is discussed.

B. MUTYH-ASSOCIATED POLYPOSIS

MUTYH-associated polyposis (MAP) is an autosomal recessive cancer predisposing syndrome found in 10-20% of patients with polyposis. The MUTYH gene is located at chromosome 1 locus, lp34 and has 16 exons. MUTYH is a base-excision repair gene involved in oxidative DNA damage repair.

Patients with MAP have a variable colonic phenotype but usually present with mild polyposis in the third and fourth decade of life. Hyperplastic polyps and sessile serrated adenomas also occur in MAP. The risk of CRC in MAP is significantly increased (75.4% and 71.7% for males and females, respectively).[32-36]

Gastric and duodenal polyps are found in 11% and 17% of MAP patients, respectively, and the life time risk of duodenal cancer is estimated around 4%. In addition, an increased risk has been reported for various cancers including ovarian, bladder, breast and endometrial cancer. Sebaceous gland tumors (adenomas, epitheliomas and carcinomas) are found in about 2% of MAP patients. In addition, benign adrenal lesions, thyroid nodules, jawbone cysts, and congenital hypertrophy of the retinal pigment epithelium have been reported.[35–37]

Recently, a study revealed a high frequency of Barrett's esophagus (BE) in patients with FAP.[38] BE is characterized by replacement of the normal squamous epithelium with columnar epithelium and is the only known precursor lesion of esophageal adenocarcinomas which is associated with gastro-esophageal reflux disease (GERD) and an increased incidence of colorectal adenomas.[39–42] It is

unknown whether BE is also more frequent in MAP patients. In **chapter 4**, we therefore studied the prevalence of BE in a large cohort of patients with MUTYH-associated polyposis and APC-associated adenomatous polyposis.

PART II: CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY (CMMRD)

Lynch Syndrome is an autosomal dominant disorder caused by a defect in one of the DNA mismatch repair genes, MLH1, MSH2, MSH6 and PSM2.[43] Homozygous and compound heterozygous pathogenic variants in these genes result in a rare cancer predisposition syndrome called constitutional mismatch repair deficiency (CMMRD).

Tumor spectrum

Patients with CMMRD develop hematological malignancies and brain tumors in the first decade of life. Malignancies of the digestive tract including CRC and small bowel tumors as well as lynch syndrome tumors such as endometrial cancers and urinary tract malignancies are diagnosed in the second and third decade of life. Non-malignant lesions may include café-au-lait macules (CALMs), mild immunoglobulin deficiencies and congenital malformations.[44,45]

Surveillance programs

Surveillance protocols have been established which has resulted in improved care for patients with various hereditary CRC syndromes.[46–48] Also, follow-up of a family with CMMRD over 10 years has proved to be effective and resulted in diagnosis of fifteen tumors.[49] However, until recently, no formal guidelines for surveillance and management of CMMRD, were available.

In 1968, a set of criteria was proposed by the WHO that should be met prior to the implementation of screening programs. These criteria include: (a) cancer should be a common problem in the target group of surveillance; (b) the natural course of the cancers should be known; (c) screening tests should be available with high sensitivity and specificity and the tests should be acceptable for the patients; (d) an effective treatment should be available after detection of the tumor; (e) there should be evidence that screening leads to diagnosis of cancer

at an early stage and to improvement of prognosis; (f) finally, the surveillance protocol should be cost-effective.[50]

In **chapter 5**, we reviewed the literature and collected data on the tumor spectrum, the clinical presentation and the natural course of the most common cancers in CMMRD including brain tumors, digestive tract cancers and hematological cancers. We then evaluated whether surveillance for various cancers complied with the above-mentioned criteria. Based on this review and discussions among the members of the European collaborative group (Care for CMMRD (C4CMMRD)), we developed guidelines for surveillance and management of patients with CMMRD.

The C4CMMRD group established a European CMMRD patient database at the Gustave Roussy Cancer Campus in Villejuif, France. The aim of this registry was collecting prospective data to evaluate the outcome and effectiveness of the surveillance protocol in CMMRD patients. In **chapter 6,** the results of surveillance of CMMRD patients that participated in the program are reported.

AIMS OF THIS THESIS

- To assess whether known CRC-associated SNPs influence the disease phenotype in patients with a germline pathogenic variant in APC.
- To investigate the occurrence of extracolonic malignancies and benign tumors in a large series of patients with FAP with a proven APC pathogenic variant known from the Dutch polyposis registry and to evaluate whether these extracolonic malignancies are an important cause of death.
- To assess the prevalence of Barrett's esophagus and esophageal adenocarcinomas by reviewing the endoscopy reports in a large cohort of patients with FAP and MAP.
- To develop a surveillance program to detect the most common cancers at an early or premalignant stage in patients with CMMRD
- To assess the effectiveness of the C4CMMRD surveillance program and discuss possible improvements of the protocol.

REFERENCES

1. Guttmacher, A. E., Collins, F. S., Lynch, H. T. & de la Chapelle, A. Hereditary colorectal cancer. *N Engl J Med* **348**, 919–932 (2003).
2. Jelsig, A. M. *et al.* Novel Genetic Causes of Gastrointestinal Polyposis Syndromes. *Appl Clin Genet* **14**, 455–466 (2021).
3. Galiatsatos, P. & Foulkes, W. D. Familial adenomatous polyposis. *Am J Gastroenterol* **101**, 385–398 (2006).
4. Hes, F. J. *et al.* Somatic APC mosaicism: an underestimated cause of polyposis coli. *Gut* **57**, 71–76 (2008).
5. Aretz, S. *et al.* Somatic APC mosaicism: a frequent cause of familial adenomatous polyposis (FAP). *Hum Mutat* **28**, 985–992 (2007).
6. Bülow, S. Results of national registration of familial adenomatous polyposis. *Gut* **52**, 742–746 (2003).
7. Groen, E. J. *et al.* Extra-intestinal manifestations of familial adenomatous polyposis. *Ann Surg Oncol* **15**, 2439–2450 (2008).
8. Barrow, P., Khan, M., Lalloo, F., Evans, D. G. & Hill, J. Systematic review of the impact of registration and screening on colorectal cancer incidence and mortality in familial adenomatous polyposis and Lynch syndrome. *Br J Surg* **100**, 1719–1731 (2013).
9. Belchetz, L. A., Berk, T., Bapat, B. V., Cohen, Z. & Gallinger, S. Changing causes of mortality in patients with familial adenomatous polyposis. *Dis Colon Rectum* **39**, 384–387 (1996).
10. de Campos, F. G. C. M. *et al.* Evaluating causes of death in familial adenomatous polyposis. *J Gastrointest Surg* **14**, 1943–1949 (2010).
11. Kinzler, K. W. *et al.* Identification of FAP Locus Genes from Chromosome 5q21. *Science (1979)* **253**, 661–665 (1991).
12. Fearnhead, N. S., Britton, M. P. & Bodmer, W. F. The ABC of APC. *Hum Mol Genet* **10**, 721–733 (2001).
13. Goss, K. H. & Groden, J. Biology of the adenomatous polyposis coli tumor suppressor. *J Clin Oncol* **18**, 1967–1979 (2000).
14. Sieber, O. M., Tomlinson, I. P. & Lamlum, H. The adenomatous polyposis coli (APC) tumour suppressor--genetics, function and disease. *Mol Med Today* **6**, 462–469 (2000).

15. Nieuwenhuis, M. H. & Vasen, H. F. A. Correlations between mutation site in APC and phenotype of familial adenomatous polyposis (FAP): a review of the literature. *Crit Rev Oncol Hematol* **61**, 153–161 (2007).
16. Nieuwenhuis, M. H. *et al.* Genotype predicting phenotype in familial adenomatous polyposis: a practical application to the choice of surgery. *Dis Colon Rectum* **52**, 1259–1263 (2009).
17. Yanaru-Fujisawa, R. *et al.* Impact of Phospholipase A2 group IIa gene polymorphism on phenotypic features of patients with familial adenomatous polyposis. *Dis Colon Rectum* **50**, 223–231 (2007).
18. Houlston, R., Crabtree, M., Phillips, R., Crabtree, M. & Tomlinson, I. Explaining differences in the severity of familial adenomatous polyposis and the search for modifier genes. *Gut* **48**, 1–5 (2001).
19. Crobtree, M. D. *et al.* Analysis of candidate modifier loci for the severity of colonic familial adenomatous polyposis, with evidence for the importance of the N-acetyl transferases. *Gut* **53**, 271–276 (2004).
20. Crabtree, M. D. *et al.* Explaining variation in familial adenomatous polyposis: relationship between genotype and phenotype and evidence for modifier genes. *Gut* **51**, 420–423 (2002).
21. Moser, A. R. *et al.* ApcMin: A mouse model for intestinal and mammary tumorigenesis. *Eur J Cancer* **31**, 1061–1064 (1995).
22. Talseth-Palmer, B. A. The genetic basis of colonic adenomatous polyposis syndromes. *Hered Cancer Clin Pract* **15**, 5 (2017).
23. Kwong, L. N. & Dove, W. F. APC and its modifiers in colon cancer. *Adv Exp Med Biol* **656**, 85 (2009).
24. Oikarinen, S. I. *et al.* Genetic mapping of Mom5, a novel modifier of ApcMin-induced intestinal tumorigenesis. *Carcinogenesis* **30**, 1591–1596 (2009).
25. Otterpohl, K. L. & Gould, K. A. Genetic dissection of the Mom5 modifier locus and evaluation of Mom5 candidate genes. *Mamm Genome* **26**, 235–247 (2015).
26. Dietrich, W. F. *et al.* Genetic identification of Mom-1, a major modifier locus affecting Min-induced intestinal neoplasia in the mouse. *Cell* **75**, 631–639 (1993).
27. Watson, A. J. M. & Collins, P. D. Colon cancer: a civilization disorder. *Dig Dis* **29**, 222–228 (2011).

28. Wen, J., Xu, Q. & Yuan, Y. Single nucleotide polymorphisms and sporadic colorectal cancer susceptibility: A field synopsis and meta-analysis. *Cancer Cell Int* **18**, 1–14 (2018).
29. Groen, E. J. *et al.* Extra-intestinal manifestations of familial adenomatous polyposis. *Ann Surg Oncol* **15**, 2439–2450 (2008).
30. Vasen, H. F. A. *et al.* The value of screening and central registration of families with familial adenomatous polyposis. A study of 82 families in The Netherlands. *Dis Colon Rectum* **33**, 227–230 (1990).
31. Heiskanen, I., Luostarinen, T. & Järvinen, H. J. Impact of screening examinations on survival in familial adenomatous polyposis. *Scand J Gastroenterol* **35**, 1284–1287 (2000).
32. Theodoratou, E. *et al.* A large-scale meta-analysis to refine colorectal cancer risk estimates associated with MUTYH variants. *Br J Cancer* **103**, 1875–1884 (2010).
33. Tenesa, A. *et al.* Association of MUTYH and colorectal cancer. *Br J Cancer* **95**, 239–242 (2006).
34. Win, A. K. *et al.* Risk of Colorectal Cancer for Carriers of Mutations in MUTYH, with and without a Family History of Cancer. *Gastroenterology* **146**, 1208 (2014).
35. Nielsen, M., Infante, E. & Brand, R. MUTYH Polyposis. *GeneReviews®* (1993).
36. Nielsen, M., Morreau, H., Vasen, H.F.A. & Hes, F.J. MUTYH-associated polyposis (MAP). *Crit Rev Oncol Hematol* **79**, 1–16 (2011).
37. Vogt, S. *et al.* Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. *Gastroenterology* **137**, (2009).
38. Gatalica, Z., Chen, M., Snyder, C., Mittal, S. & Lynch, H. T. Barrett's esophagus in the patients with familial adenomatous polyposis. *Fam Cancer* **13**, 213–217 (2014).
39. Shaheen, N. J. *et al.* Diagnosis and Management of Barrett's Esophagus: An Updated ACG Guideline. *Am J Gastroenterol* **117**, 559–587 (2022).
40. Hvid-Jensen, F., Pedersen, L., Drewes, A. M., Sørensen, H. T. & Funch-Jensen, P. Incidence of adenocarcinoma among patients with Barrett's esophagus. *N Engl J Med* **365**, 1375–1383 (2011).
41. Jankowski, J. A., Harrison, R. F., Perry, I., Balkwill, F. & Tselepis, C. Barrett's metaplasia. *The Lancet* **356**, 2079–2085 (2000).

42. Kumaravel, A. *et al.* Higher prevalence of colon polyps in patients with Barrett's esophagus: a case-control study. *Gastroenterol Rep (Oxf)* **2**, 281–287 (2014).
43. Biller, L. H., Syngal, S. & Yurgelun, M. B. Recent advances in Lynch syndrome. *Fam Cancer* **18**, 211–219 (2019).
44. Wimmer, K. *et al.* Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). *J Med Genet* **51**, 355–65 (2014).
45. Durno, C. A. *et al.* Phenotypic and genotypic characterisation of biallelic mismatch repair deficiency (BMMR-D) syndrome. *Eur J Cancer* **51**, 977–983 (2015).
46. Vasen, H. F. A., Tomlinson, I. & Castells, A. Clinical management of hereditary colorectal cancer syndromes. *Nat Rev Gastroenterol Hepatol* **12**, 88–97 (2015).
47. Vasen, H. F. *et al.* Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut* (2008) doi:10.1136/gut.2007.136127.
48. Vasen, H. F. A. *et al.* Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut* **62**, 812–823 (2013).
49. Durno, C. A. *et al.* Oncologic surveillance for subjects with biallelic mismatch repair gene mutations: 10 year follow-up of a kindred. *Pediatr Blood Cancer* **59**, 652–656 (2012).
50. Wilson, J. M. & Jungner, Y. G. [Principles and practice of mass screening for disease]. *Bol Oficina Sanit Panam* **65**, 281–393 (1968).