# Chapter 10
# Hereditary Mixed Polyposis Syndrome

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## Introduction

Hereditary cancer syndromes are generally the result of high-penetrance germline mutations in genes that directly restrain uncontrolled growth or preserve the integrity of the genome. A number of such syndromes exist that have colorectal cancer (CRC) and/or polyps as their primary feature. Examples (with their genes) include Lynch syndrome (*MSH2, MLH1, MSH6, PMS2*), familial adenomatous polyposis (*APC*), Peutz-Jeghers syndrome (*STK11*), and juvenile polyposis syndrome (JPS) (*SMAD4, BMPR1A*), among others. Each syndrome is associated with distinctive clinical phenotypic features as well as tumors of a particular morphology [1, 2]. Hereditary mixed polyposis syndrome (HMPS) is a rare CRC syndrome that is inherited in an autosomal dominant fashion. It does not have a pathognomonic clinical phenotype, but the patients develop colorectal polyps of several different histological types, including individual tumors that combine different morphologies. HMPS polyps include atypical juvenile polyps, adenomas, and a variety of serrated/hyperplastic polyps [3].

HMPS was first described in a large Ashkenazi kindred, St. Mark's family 96 (SM96), who had a dominantly inherited predisposition to multiple large bowel polyps and early onset CRC. Many questioned whether these patients had an atypical variant of an established polyposis syndrome, or a distinct disorder [2]. The disease in this pedigree was found not to be linked to loci associated with other polyposis syndromes such as *APC* or mismatch repair genes (MMR genes) *MLH1*, *MSH2*, *MSH6*, or *PMS2*, and its phenotype did not include extracolonic features [3].

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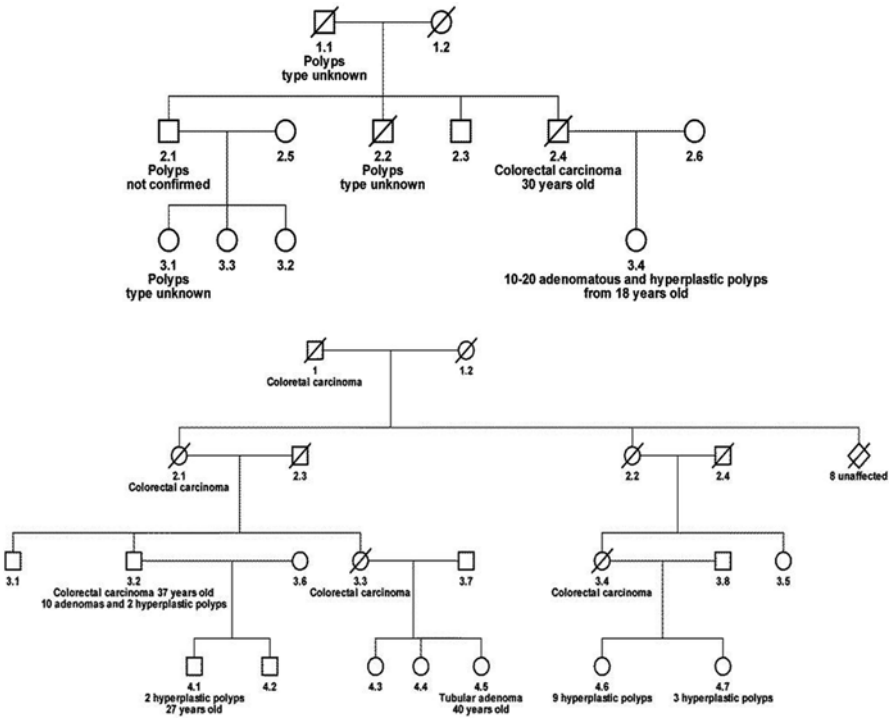


**Fig. 10.1** Pedigrees and phenotypes of some HMPS families showing variation in the phenotype and sometimes relatively mild clinical features

These findings provided support for a distinct syndrome. A molecular diagnosis was ultimately needed for the characterization of this syndrome. Initially, studies mapped the *HMPS* locus to chromosome 6q16-21 [4]. More recently, progress was made regarding the molecular mechanisms underlying HMPS showing that the HMPS gene is not located at 6q16-61 as previously thought, but at 15q13-q14 (Fig. 10.1).

## Clinico-Pathological Features of Hereditary Mixed Polyposis Syndrome

The SM96 pedigree was followed for nearly 40 years. It consisted of more than 20 second degree generation, 64 third generation, 102 fourth generation, and 42 fifth generation individuals [2]. Individuals from this pedigree presented at a median age of 40 years (range 23–65 years) [2]. Clinical presentation consisted of changed bowel habit, passing blood per rectum, abdominal pain, obstruction, or anemia [2]. The median age at diagnosis of CRC was 47 years (range 32–74 years) [2].

On colonoscopic examination, affected individuals presented with a combination of polyp histologies including atypical juvenile polyps, which are perhaps the most characteristic tumors, but also adenomatous and hyperplastic polyps. Affected individuals had no upper gastrointestinal or extraintestinal manifestations.

To describe the characteristics of polyps in individuals with HMPS, 159 from the SM96 pedigree were evaluated and classified according to the World Health Organization of Morson and Sabin [5]. Individuals with HMPS usually presented with less than 15 polyps at initial endoscopic evaluation, although the number of polyps varied among patients. The polyps were distributed throughout the colon, as were the CRCs. Metachronous and synchronous polyps of different histopathologic types were identified. Examples are shown in Fig. 10.2.

## Molecular Features and Genetics

The classification of individuals with HMPS was challenging, particularly when these individuals did not present with a characteristic phenotype and/or had synchronous and metachronous polyps of various histopathologic types. In an effort to assess whether these patients had an atypical presentation of an already established polyposis syndrome, or a distinct disorder, molecular diagnosis was needed for further classification. Initial linkage analysis on SM96 pedigree excluded most of the mutations at candidate loci, which were known to be associated with hereditary or sporadic colorectal tumors, as the cause of HMPS [2]. Linkage of the HMPS locus to the FAP locus, *APC*, as well as other candidate loci, including *MSH2*, *TP53*, and *DCC*, were excluded on the basis of logarithm of the odds (LOD) score [2], a LOD score of >3.0 conventionally being considered evidence of genetic linkage between the disease and the test loci [2].

Data from previous studies initially mapped the HMPS locus to chromosome 6q16-q21 [4]. A genetic linkage analysis was performed on 46 members of the HMPS kindred, SM96. This analysis showed that the only significant positive LOD score was found at the D6S283 locus on chromosome 6q [4]. SM96 was subsequently retested. A genome wide linkage screen was performed in the SM96 kindred, which confirmed that HMPS and 6q16-q21 alleles did not co-segregate [6]. However, the genome wide screen showed that the only site in the genome with evidence of linkage to HMPS was on chromosome 15q13-q21 [6].

Individuals from another Ashkenazi kindred SM1311 had a similar phenotypic presentation to HMPS. Affected members of SM1311 presented with polyps of multiple histopathological types and CRC, throughout the colon, without evidence of extracolonic features. Genetic linkage and mutational analysis were done to locate a novel susceptibility gene in this Ashkenazi pedigree (SM1311). Genetic linkage analysis showed evidence for a new susceptibility gene *CRAC1*, which mapped to chromosome 15q14-q22 [7]. This raised the question of whether *HMPS*

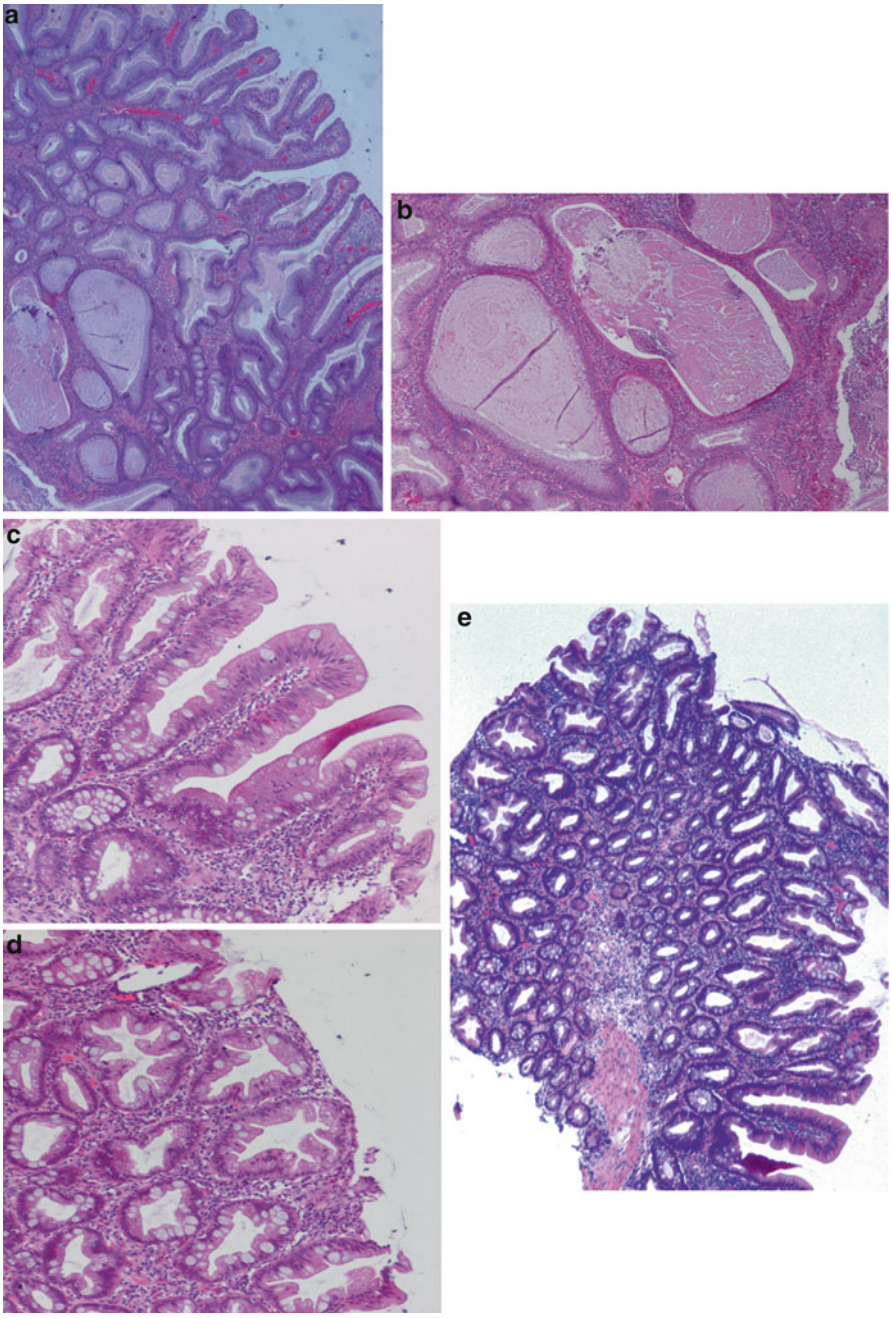


**Fig. 10.2** Histopathological features of HMPS polyps. (**a**) Mixed juvenile-hyperplastic-adenomatous polyp. (**b**) Juvenile polyp. (**c**) Adenoma with serrated features. (**d**) Hyperplastic polyp. (**e**) Mixed hyperplastic-adenomatous polyp

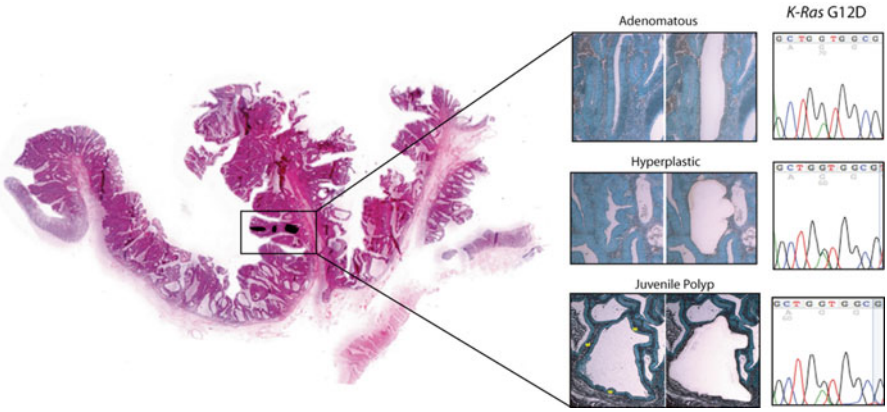


**Fig. 10.3** Somatic KRAS mutations variably present in different areas of an HMPS polyps

and *CRAC1* might be the same locus. Jaeger et al. compared the *CRAC1* and SM96 disease-associated haplotypes, and found that they were identical for markers shared within a region between microsatellite markers D15S1031 and D15S118 on chromosome 15, suggesting that the *HMPS* and *CRAC1* genes were the same [6]. Subsequently, several additional Ashkenazi families that presented with colorectal adenomas were examined (Fig. 10.1). All affected members were found to have the HMPS/CRAC1 haplotype between D15S1031 and D15S118, and this was rare in the general Ashkenazi population [6]. The data indicated that these families most likely shared an ancestral mutation that was responsible for their disease.

The causative germline mutation for HMPS was identified by Jaeger et al. The authors showed that HMPS results from an unusual duplication of approximately 40 kb upstream of the gene that encodes the bone morphogenetic protein (BMP) agonist *GREM1* [1]. This duplication, which contains a variety of gene regulatory elements, causes greatly increased *GREM1* expression and ectopic expression in the epithelium of the colon as well as the normal location in the mesenchyme. Excess GREM1 is predicted to cause reduced BMP pathway activity, thus resembling the inactivation of BMP pathway components (SMAD4 and BMPR1A) thought to underlie tumor formation in JPS [1]. The ancestral Ashkenazi HMPS duplication can be identified using a single PCR based on the finding that there exists a short unique DNA sequence between the duplicated regions. However, such testing is unlikely to be sufficient, since recently, an independent, slightly smaller duplication upstream of *GREM1* has been reported in a northern European family without known Jewish ancestry.

The molecular pathways of polyp formation and progression to cancer in HMPS are not well characterized. *GREM1* does not appear to be a tumor suppressor, but a "landscaper" gene that alters the microenvironment to make it permissive for colorectal tumorigenesis. The available evidence suggests that the initial HMPS lesion is usually a hyperplastic polyp that carries a somatically acquired *KRAS* or *BRAF* mutation (Fig. 10.3). This may become dysplastic owing to *APC* mutations

and progress to carcinoma. Whether juvenile polyps can develop without the requirement for further somatic mutations remains unclear.

## Overlap Between HMPS and Juvenile Polyposis

Given their related functional gene defects, it is perhaps not surprising that the phenotypic features of HMPS and JPS overlap, and juvenile polyps can occur in both syndromes. Such overlapping features are common in cancer syndromes. There are, however, clear differences between HMPS and JPS, including: (1) the presence of important extracolonic features in JPS; (2) the predominance of serrated/hyperplastic polyps in HMPS; (3) the generally older age of presentation in HMPS; and (4) disease prevalence. Recent claims that *BMPR1A* mutations can cause HMPS [8] have little utility, not least because HMPS patients can also present with very similar disease to patients with germline mutations in *APC and MUYTH, NTHL1, POLE, POLD1*, and the MMR genes. These syndromes are best defined by their underlying mutations, even if the phenotypic features share similarities.

## Recommendations for Surveillance in HMPS

For asymptomatic HMPS mutation carriers, the age at which screening should be started and the surveillance interval are unclear owing to the rarity of the disease and its young history as a defined entity still need to be elucidated. Existing data show that the earliest age at which polyps have been diagnosed in an affected individual was 18 years. Therefore, it might be reasonable to start screening at the age of 18 years, based on the available data [2]. Currently there are no established guidelines for surveillance. Biennial colonoscopy is recommended based on the finding that an individual from the SM96 pedigree developed 12 adenomas in a two-year interval [2]. Since half of the cancers diagnosed in SM96 were found proximal to the mid-transverse colon, colonoscopy is considered the screening modality of choice [2]. Extracolonic screening is not currently recommended. Colonoscopy appears sufficient to manage the polyp burden and risk of progression according to the limited available evidence, and prophylactic surgery is not currently recommended.

## Summary

HMPS is a Mendelian dominant CRC predisposition syndrome, characterized by multiple colorectal polyps. The distinctive clinical phenotype of polyps of mixed histopathological type is not reliably present, and mixed polyps (e.g.,

serrated + adenomatous, juvenile + adenomatous) can be present in other conditions. It is therefore recommended that duplications upstream of *GREM1* are included in gene panels for testing the Mendelian CRC genes, unless there is a sufficient clinical suspicion and a dominant pedigree of Ashkenazi origins, in which case early, focussed *GREM1* screening could be performed. Although screening and surveillance algorithms still need to be elucidated, early recognition of individuals at risk for this syndrome will potentially help decrease morbidity and mortality of CRC, as early screening implementation should be effective in detecting premalignant lesions and early stage CRC.

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