Original Article

Familial Adenomatous Polyposis: Data from the Hereditary Colorectal Cancer Registry (HCCR)

Erika Maria Monteiro Santos, RN, PhD; Fábio de Oliveira Ferreira, MD, PhD; Samuel Aguiar Junior, MD, PhD; Wilson Toshihiko Nakagawa, MD, MSc; Ademar Lopes, MD, PhD.; Arnaldo Medeiros, PhD; Benedito Mauro Rossi, MD, PhD

Hereditary Colorectal Cancer Registry, Hospital A.C. Camargo

Abstract

Family adenomatous polyposis (FAP) is a dominant autossomic disease responsible for nearly 1% of colorectal cancer (CRC) cases caused by mutations in gene APC and nearly complete penetrance. The identification of germinative mutations can be useful in the definition of the therapeutic conduct by means of the correlation genotype-phenotype. **Objective:** To describe clinical and molecular characteristics of families with FAP or attenuated FAP. Method: The study included families registered in the Hereditary Colorectal Cancer Registry of A.C.Camargo Hospital. Cancer records were registered and heredograms were created. Data were collected and stored in a database. **Results:** From 1992 to 2007 22 families were registered that had FAP, 16 with classic FAP, nine with Gardner Syndrome, and 6 with attenuated FAP. From 604 individuals, 120 had polyposis, 62 CRC, 10 desmoid tumors, three breast tumors, two tumors of the stomach, two thyroid tumors and one with prostate tumor. From 22 families, three were submitted to molecular analysis and mutations were identified in gene APC. **Discussion:** Half of the individuals presented CRC concomitant to polyposis, which can indicate a late diagnostic of the disease; three identified mutations presented correlations genotype-phenotype as predicted by the literature. Follow-up of patients with FAP, although they account for less than 1% of CRC cases, is vital for early cancer diagnosis.

Keywords: Hereditary. Adenomatous polyps. Colorectal neoplasms.

Introduction

Family adenomatous polyposis (FAP) is a dominant autossomic disease responsible for nearly 1% of colorectal cancer (CRC) cases. It has as clinic diagnostic criterion the presence of more than a hundred adenomatous polyps in the colon. It is associated to germinative mutations in *APC* gene, a tumor-suppressor gene located in the long arm of chromosome 5 (5q21).[1]

In 1882, from two reports of individuals with CRC at a young age, William Harrison Cripps suggested the existence of FAP and said it was a rare condition.[2] In 1920, Niemack reports a case in which a father and a daughter had polyposis and suggests the existence of an inherited condition.[3] Lockhart-Mummery described FAP in 1925, besides organizing the first register of families with the disease.[4] In 1951, Gardner proposes that only one gene causes the disease, which presents dominant autossomic inheritance.[5] In 1986 a patient with FAP was described that presented a deletion on part of the long arm of chromosome 5,[6] and in the same year, based on ligation analysis the region was located as being 5q21-22,[7]

Correspondence
Erika Maria Monteiro Santos
Hospital A.C. Camargo
Rua Professor Antonio Prudente 211
015090010 São Paulo Brazil
Phone: 55 11 21895000 ext 1080
E-mail: emonteiro@hcancer.org.br

and subsequently in 1991 gene *APC* was cloned.[8-9]

The gene presents 15 exons.[4,7] Exon 15 represents more than 75% of the codifying sequence of the gene, and is a more frequent target than somatic and germinative mutations.[4]

The mutation in gene *APC* predisposes the intestinal epithelium to develop at an early age multiple adenomatous polyps (from a hundred to thousands), which must be removed for preventing malignant transformation from the third to the fourth decades of life.[1,10]

Besides the development of intestinal adenomas, and CRC, there are extracolonic benign and malignant manifestations associated to the disease. When these extracolonic manifestations are present, we may also call this Gardner's Syndrome, whereas the association of colorectal adenomas and tumors of the central nervous system is called Turcot's syndrome.[1]

Benign manifestations include upper gastrointestinal adenomas, in the stomach and duodenum, hepatic, thyroidal and adrenal; osteomas; desmoid tumors; anomalous teething; epidermoid cysts and CHRPE (congenital hypertrophy of the retinal pigment epithelium).[1]

Malignant neoplasic manifestations include, besides CRC, periampullary carcinoma, gastric carcinoma, desmoid tumors, generally abdominal, located in the mesentery or mesocolon, adrenal carcinoma, colangiocarcinoma, hepatoblastoma, glioblastoma and medulloblastoma.[1,10]

The identification of the germinative mutation can be useful in the definition of the therapeutic conduct and in the selection of individuals for screening. This paper aims to characterize a group of individuals pertaining to Brazilian families with FAP as for the frequency of clinical manifestations. We also present the molecular analysis of three probands.

Methods

Families were included that were assisted by the Hereditary Colorectal Cancer Registry (HCCR) of A.C.Camargo Hospital. HCCR was established in 1992, and aims the reduction of morbidity and mortality associated to colorectal cancer in individuals with hereditary predisposition to cancer.[11]

After the identification of an individual with more than 10 adenomatous polyps, he is invited to participate in the register. Family history is examined and a heredogram is created with standardized symbols.[11]

For this paper patients were selected with family adenomatous polyposis (individuals with 100 or more adenomatous polyps) or attenuated family adenomatous polyposis (individuals with 10 to 100 adenomatous polyps).

Data were collected from the information contained in the heredogram. We present the total number of subjects, the number of individuals with polyposis and colorectal cancer, the number of individuals with desmoid tumors, and the number of individuals with other tumors.

From the selected families, three were submitted to molecular analysis. In two we did a protein truncated test and manual sequencing, and in one did automatic sequencing.[12-13] The characteristics of the family history of these families are compared with the type of identified mutation.

Results

From 1992 to 2007, 22 families were identified. From those, 16 had FAP and six had attenuated FAP. Table 1 presents the characteristics of the family history of the selected families.

From the total of 16 families with FAP, nine had extracolonic manifestations that characterized it as Gardner's Syndrome.

From 604 individuals, 120 had intestinal polyposis, and 62 (51.6% of the individuals with polyposis) had colorectal cancer. From the individuals with cancer colorectal, 45 died. From the total, 10 individuals (1.65 %) had desmoid tumors, and from those five died due to the disease. Among desmoid tumors, only one was diagnosed simultaneously to the diagnosis of polyposis, whereas the others were diagnosed after colectomy/protocolectomy. There were also three breast tumors, two tumors of the stomach, two tumors of the thyroid, a prostate tumor, a melanoma and a head and neck tumor. We describe here the families that were submitted to molecular analysis.

Family 1

Family with 60 individuals in three generations, having 10 affected individuals. The phenotype is of profuse polyposis, of aggressive behavior, with intestinal adenomas developing in adolescence, and the malignant transformation of the adenomas occurring at an average 27.6 years of age (from 10 individuals with polyposis, seven had colorectal cancer). There are extracolonic manifestations (two individuals with osteomas, one with a desmoid tumor, and one with gastric and duodenal

Table 1 - Family history of the 22 families registred in the HCCR

Family	Classification	Number of Individuals	Individuals with Polyposis	Individuals with CRC	Individuals with Desmoid Tumor	Individuals with other tumors
1	Gardner	60	10	7	1	-
2	Gardner	85	18	12	1	Breast (1) Melanoma (1) Head and Neck (1)
3	Gardner	25	1	-	-	Prostate (1)
4	Classical FAP	10	4	2	-	-
5	Classical FAP	11	6	5	-	-
6	Gardner	66	13	7	3	Gastric (1)
7	Classical FAP	13	3	1	-	Breast (1)
8	Classical FAP	36	17	8	-	Breast (1)
9	Gardner	10	2	1	1	-
10	Classical FAP	24	5	4	-	-
11	Gardner	43	8	5	2	-
12	Gardner	48	13	4	3	Thyroid (1)
13	Gardner	17	1	-	1	-
14	Classical FAP	16	1	-	-	-
15	Classical FAP	7	5	2	-	-
16	Gardner	22	7	2	-	Thyroid (1)
17	Attenuated FAP	23	1	1	-	-
18	Attenuated FAP	36	1	1	-	-
19	Attenuated FAP	18	2	1	-	-
20	Attenuated FAP	28	7	2	-	Gastric (1)
21	Attenuated FAP	3	1	1	-	-
22	Attenuated FAP	10	1	1	-	-

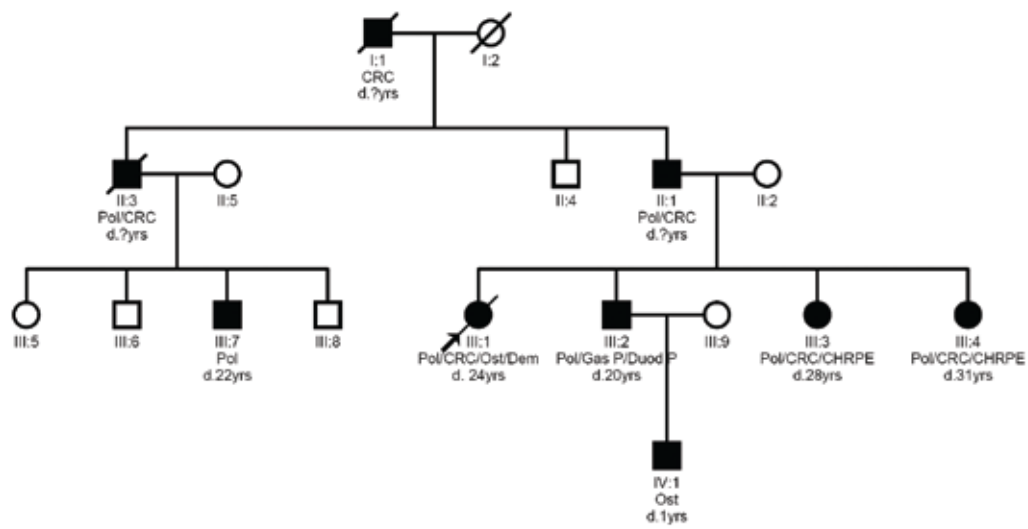

Figure 1 - Heredogram from family 1. Pol- large bowel polyposis; CRC - colorectal cancer; Gas P - gastric polyposis; Duod P - small bowel polyposis; Ost - osteoma/ Dem - desmoid tumor; CHRPE - congenital hypertrophy of the retinal pigment epithelium

polyposis). Figure 1 presents part of the the heredogram of the family.

The mutation was identified in gene *APC* in exon 15, codon 1.291. In this family an insertion of "T"

Figure 2 - Scheme representing the mutation identified in family 1

is observed causing a frameshift mutation some codons latter in the sequence. (Figure 2).[12-13]

Family 2

Family with 85 members distributed in five generations, from which 21 were affected (polyposis or cancer). From 18 individuals with polyposis, 12 had CRC. Polyposis is scattered, limited to the colon, and does not reach the rectum; intestinal polyps were diagnosed at 25 years of age, and the diagnosis of colorectal cancer at 40 years of age. In this family an individual had a desmoid tumor after the development of CRC, and an individual had gastric polyps. Besides, a female patient with polyposis and colorectal cancer had a breast tumor at 45 years of age. A female patient had two melanomas and, finally, a male patient had a head and neck tumor. Figure 3 presents parts of the heredogram of family 2.

The mutation was identified in gene *APC* in exon 13, codon 564, type nonsense (CGA (Arg)> TGA (stop).

Family 3

13-year-old patient, with polyposis, with no family history (parents and brothers were submitted to retossigmoidoscopy). The polyposis is profuse, with aggressive behavior, and development in childhood, with adenomas from the stomach to the rectum. (Figura 4)

It is a de novo mutation in gene *APC,* frameshift, in exon 15, with deletion of five bases (AAAGA) from codon 1.309, with *stop codon* immediately after, in codon 1.312.

Discussion

FAP accounts for nearly 1% of CRC cases,[10] but the identification of affected patients by clinical and/ or molecular diagnosis contributes to the reduction of

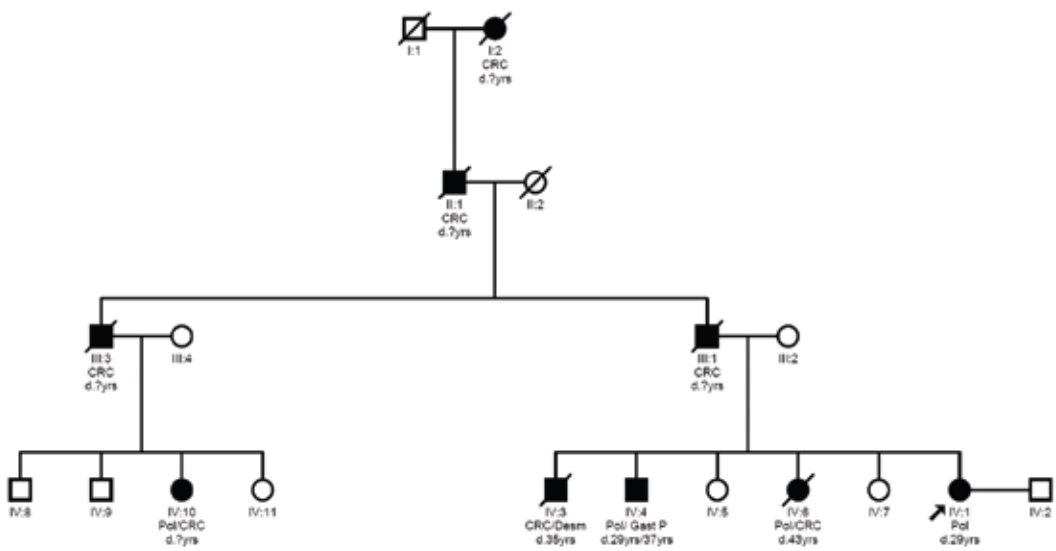

Figure 3 - Heredogram from family 2. Pol- large bowel polyposis; CRC - colorectal cancer; Desm - desmoid tumor.

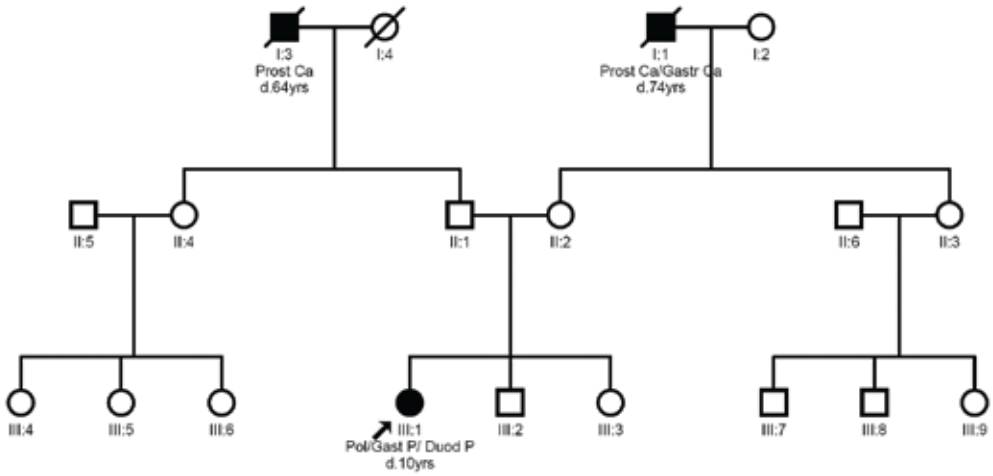

Figure 4 - Heredogram from family 3. Pol- large bowel polyposis; Gas P - gastric polyposis; Duod P - small bowel polyposis; Prost Ca - prostate cancer; Gast Ca - gastric cancer

morbidity and mortality when they were associated to the disease, as soon as the penetrance is near to 100%. The identification of these individuals must lead to the continuation in institutions specialized with experience in the individuals' handling with FAP.

FAP diagnosis is based in the presence of more than 100 adenomatous polyps in the colon. However, Vasen et al.[14] point out that the diagnosis of attenuated FAP (AFAP) is more complex. Although criteria for AFAP clinical diagnosis have been proposed, there is not an established criterion such as there is for FAP.

Most of individuals with FAP develop the polyps in the childhood or adolescence, and when the bowel is not removed they develop CRC.

In this sample, from the total of individuals with polyposis, 51.6% presented synchronous CRC at diagnostic. Most of them are the probands, or individuals with no follow-up in which the disease was diagnosed by symptoms. Bulow[15] noticed that 67% of probands of the national register of polyposis had colorectal cancer concomitantly with FAP, whereas this frequency of 3% in individuals with follow-up. This change has a significant impact in mortality rates associated with FAP, and shows the importance of the registers of hereditary cancer in the follow-up of these individuals.[15,16]

The main cause of death of these individuals was CCR followed by desmoid tumors, which corresponds to observations of other series.[16-17]

Gurbuz et al.[18] analyzed data of Johns Hopkins Polyposis Registry and verified that 10% of patients with FAP had desmoid tumors. When they compared this with the incidence of desmoid tumors in the general population, the authors observed it to be 852 times higher. Desmoid tumors are a challenge in management, on account of the difficulty in carrying out surgeries with appropriate margins. Non-hormonal and anti-estrogenic anti-inflammatory agents are used both separately and in combination. Cytotoxic chemotherapy is also used, specially in unresecable tumors that do not respond therapy with anti-inflammatory and anti-estrogenic agents.[14,19-20]

Since most data come from in family history, the evaluation of the incidence of other extracolonic manifestations, such as CHRPE (congenital hypertrophy of the retinal pigment epithelium), osteomas, gastric and duodenal polyps was not possible, for most reports include only information on polyposis, CCR and desmoid tumors. CHRPE is a benign manifestation of polyposis and its incidence varies from 29 to 92%.[21-22]

Polyps in the upper gastrointestinal tract are also common, and they may affect from 24% to 96% of FAP patients.[23] In our sample, two individuals from different families had with stomach cancer. It is not possible to say if these tumors were extracolonic manifestations of FAP or only sporadic, due to the high incidence of cancer of the stomach in Brazil and the absence of diagnostic endoscopy. According to Vasen et al.[14] cases of gastric cancer were described in Japan and Korea, but no increase was observed in the risk of gastric cancer in samples of Western countries, where a broader investigation is necessary for confirming these findings.

Two individuals had carcinoma of thyroid and

intestinal polyposis. Both were female, and with diagnosis of the disease before 30 years of age. Thyroid cancer in FAP is a rare extracolonic manifestation, affecting from 1% to 2% of patients.[24-26] It affects predominantly women and, on average, at 32 years old (24-26), a characteristics also observed in this sample.

We also observed cases of melanoma, head and neck, breast, and prostate cancer in these families. These tumors are not part of the syndrome, but emphasize the need for surveillance of sporadic tumors in families having hereditary syndromes of predisposition to cancer.

In 1994, the mutation which caused FAP was identified in a family of the HCCR. It was the first mutation to be identified in gene *APC* in a Brazilian family having FAP[12-13] and published.

Of three reported mutations, two are nonsense and one frameshift, which is compatible with the literature. Most mutations (95%) are nonsense or frameshift, resulting in a truncated protein.[27] Mori et al.[28] reported that 65% of mutations in *APC* is observed in the so called mutation cluster region (MCR) located between codons 1.286 and 1.513.

Also we could notice that two families had profuse polyposis and mutations were identified in codons 1.291 and 1.309, respectively.

The correlation between genotype and phenotype is described as present in FAP.[4] Nagase et al.[29] evaluated 22 patients with FAP and divided them in two groups: one with profuse polyposis (more than 5.000 polyps) and other with scattered polyposis (less than 5.000 polyps). Patients in the group of scattered polyposis presented mutations between codons 213 and 1.249 and between codons 1.465 and 1.597. Patients with profuse polyposis presented mutations between codons 1.255 and 1.467.[29] Mutation in codon 1.309 is connected to an aggressive polyposis with early manifestation of adenomas and cancer.[29] Friedl et al.[30-31] verified that patients with mutation in codon 1309 had intestinal symptoms nearly 10 years before patients with mutation in other places.

The extracolonic manifestations also present a correlation genotype-phenotype. Wallis et al.[32] noticed that 15% of the individuals with mutation between codons 177 and 452 had extracolonic manifestations, a frequency inferior to 26% and 87% observed in individuals with mutation between codons 457 and 1309 and 1395 and 1493, respectively.

CHRPE, for example, is associated to mutations between codons 457 and 1444, whereas mandibular osteomas, desmoid tumors and duodenal polyps are observed in individuals with mutation near to codon 1400.[22,30-31]

Intrafamily variability observed in FAP cannot be explained only based on the location of the mutation in gene *APC*, and there are suggestions that modifier genes may be responsible for this variation.[31]

The identification of the mutation has as main implications the possibility of better selecting individuals who must have endoscopic follow up and helping the decision about the surgical procedure for treating adenomas. According to Church,[33] besides the observation of the phenotype and the conditions of the patient, mutations in exons 3 and 4 of gene *APC* can indicate the possibility of doing a total colectomy with ileorectal anastomosis, saving the rectum, whereas mutations as 1.309 must indicate total proctocolectomy with ileal pouch and lower anastomosis.

The genetic test for predisposition to cancer is not indicated for non-adult patients, but FAP is one of the exceptions. As the manifestation happens in puberty and there is the possibility of diagnosing hepatoblastoma in childhood, the test may be indicated for non-adults. The decision as to the test may be given by the legal guardian of the child, but depending on its capacity of understanding she must take parte in the discussion.[34-35]

It must be pointed out that the genetic predisposition test can be useful in the clinical handling of patients, but its implications for individuals and families must be discussed with involved individuals during pre-test and post-test genetic counseling. Genetic counseling is vital in handling families.

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