Review

The value of opthalmic examinations in familial adenomatous polyposis syndrome screening

K.H. Katsanos[1], Marika Syrrou[2], E.V. Tsianos[3]

SUMMARY

The dominantly inherited gastrointestinal polyposis syndromes are divided into adenomatous and hamarto-matous varieties, depending on the histology of the polyps.

The justification for screening as a method of cancer prevention in inherited gastrointestinal polyposis syndromes is well established as the cancer risk in FAP patients presenting with symptoms varies from 32%-57%.

Screening methods in inherited polyposis syndromes include non-invasive screening methods such as family tree, clinical examination for extracolonic malignancies, dilated fundus examination (CHRPE), DNA analysis and APC gene mutations.Invasive screening methods include endoscopy, small bowel radiography and fundus angiography.

Congenital hypertrophy of retinal pigment epithelium (CHRPE) has been reported in association with familial adenomatous polyposis and Gardner syndrome and the presence of multiple CHRPE lesions has been correlated with the presence and development of polyposis in these conditions. When present, CHRPE is a reliable clinical marker. In CHRPE-negative families, negative ophthalmic examinations are of no diagnostic value.

Opthalmoscopy facilitates genetic analysis because the status of CHRPE considerably facilitates locating the mutation in genetic diagnostics. Thus, the combination of an ophthalmic examination with a DNA analysis and endoscopy improves the risk assessment for carriers of inherited gastrointestinal polyposis syndromes.

Children of affected patients should undergo flexible proctosigmoidoscopy beginning at 10 to 12 years of age and repeated every 1 or 2 years until 35 years of age; thereafter examinations should be performed every 3 years. Because the age at which colorectal polyps develop varies, screening by repeated bowel examination is necessary from puberty until at least 40 years of age before a family member can be considered unaffected.

Basically, there are two surgical options for patients with inherited gastrointestinal polyposis syndromes; subtotal colectomy with ileorectostomy on the one hand, or total colectomy with pouch-anal anastomosis or terminal ileostomy on the other.

Key words: FAP (familial adenomatous polyposis), APC gene (adenomatous polyposis coli), CRC (colorectal cancer), CHRPE (congenital hypertrophy of retinal pigment epithelium), inherited polyposis syndromes.

[1]House Officer in Gastroenterology, [1]Division of Internal Medicine (Hepato-Gastroenterology Unit) and [2]Assistant Professor in Biology Laboratory of Biology, [3]Professor of Medicine, [3]Medical School, University of Ioannina, Greece

Author responsible for correspondence and reprints:

Epameinondas V. Tsianos, Professor of Medicine, Department of Internal Medicine, University of Ioannina, Medical School, Leoforos Panepistimiou 45 110 Ioannina, Tel: 0030.26510.97501, Fax: 0030.26510.97016, email: etsianos@cc.uoi.gr

Abbreviations used in the text:

CHRPE(congenital hypertrophy of retinal pigment epithelium),

RPE (Retinal pigment epithelium)

ECM(extracolonic malignancies),

APC(adenomatous polyposis coli),

CRC(colorectal cancer),

HFAS (hereditary flat adenoma syndrome),

FAP(familial adenomatous polyposis),

ERG(electroretinography),

IAPS (Inherited adenomatous polyposis syndromes).

1. CLASSIFICATION OF THE INHERITED POLYPOSIS SYNDROMES

The dominantly inherited gastrointestinal polyposis syndromes are divided into adenomatous and hamartomatous varieties, depending on the histology of the polyps (Table 1).

The adenomatous polyposis syndromes include familial adenomatous polyposis coli (FAP) syndrome and familial hereditary nonpolyposis colorectal cancer syndrome (HNPCC or Lynch syndrome).

Within the spectrum of *FAP syndrome*, the typical form of FAP syndrome, Gardner's syndrome, attenuated familial polyposis syndrome and several families with Turcot syndrome (those with APC gene mutation) are included. Diagnosis of familial adenomatous polyposis is contingent on a histopathologic diagnosis of the colorectum, as agreed by an international group of FAP registries in 1987.[1-2] The term "familial adenomatous polyposis" (FAP) is used to designate that pathologic condition of the colon in which large numbers (usually hundreds) of adenomatous neoplasms, generally benign and of variable size, arise from the mucosal epithelium of the entire large intestine. It is also used to designate that condition in which there is a dense segmental development of such tumours, the remaining mucosa

Table 1. Inherited polyposis syndromes

1. Adenomatous polyposis syndromes
  a. Familial adenomatous polyposis (FAP) syndromes
    - Typical FAP syndrome (including HFAS)
    - Gardner's syndrome
    - Turcot's syndrome (families with APC mutation)
    - Attenuated adenomatous polyposis coli
  b. Hereditary Nonpolyposis Colorectal Cancer
    (HNPCC or Lynch syndrome)
    - Muir-Torre syndrome
    - Turcot's syndrome (families with hMLH1 & hPMS2 mutation)

2. Hamartomatous polyposis syndromes
  - Peutz-Jeghers syndrome
  - Familial juvenile polyposis
  - Cowden's disease
  - Intestinal gaglioneuromatosis/neuroinomatosis
  - Ruvalcaba-Myhre-Smith syndrome
  - Devon family syndrome

Adopted from Textbook of Gastroenterology ,T.Yamada (Ed), Lippincott 3d edition Philadelphia 1999, p. 1995-2022

being free of neoplastic change. Most experienced observers feel that these changes are closely related, the segmental form probably representing a stage in the development of involvement of the entire colon. More recently, numerous observers have suggested that at least 10 per cent (and probably more) of the same individuals will have a variety of tumours, frequently malignant, in many other primary anatomic sites.[3]

The familial hereditary nonpolyposis colorectal cancer syndrome (HNPCC or Lynch syndrome) group includes also Muir-Torre syndrome and several families with Turcot's syndrome (those with hMLH1 and hPMS2 gene mutations). Hereditary nonpolyposis colorectal cancer (CRC) is characterized by early onset colonic cancer occurring with a dominant pattern of inheritance. It is further divided into two types: Lynch syndrome type I (hereditary site-specific colon cancer) and Lynch syndrome type II (cancer family syndrome, where colon cancer is associated with other extracolonic adenocarcinomas, particularly endometrial adenocarcinoma). In hereditary nonpolyposis colorectal cancer the term nonpolyposis is a misnomer, since adenomatous polyps are indeed found; however they are few in number as contrasted with hundreds to thousands of polyps in familial adenomatous polyposis coli or Gardner's syndrome.[4]

The hereditary flat adenoma syndrome (HFAS) has been proposed to be a variant of FAP or a third distinct group (except FAP and HNPCC) of inherited adenomatous polyposis syndromes. In HFAS the principal phenotypic marker is multiple colonic adenomas (usually less than 100) with a tendency for proximal location. Colon cancers typically develop in middle age and show no unusual histologic features. The HFAS is contrasted with hereditary nonpolyposis colorectal cancer (CRC) and FAP and is shown to be distinct from both in the numbers and distribution of colonic adenomas and the typical age of cancer diagnosis. HFAS may represent one part of a continuum of progressively more severe mutations cumulating in FAP variants with early onset of florid polyps and CRC.[5]

Hamartomatous polyposis syndromes include Peutz-Jeghers syndrome (P-J s.), familial juvenile polyposis, Cowden's syndrome, intestinal gaglioneuromatosis, neuroinomatosis and Ruvalcaba-Myhre-Smith syndrome[6].

2. GENETICS ASPECTS OF THE INHERITED POLYPOSIS SYNDROMES

FAP is an autosomal dominantly inherited disorder with an 80-100% penetrance and results from inactivating

germ line mutations of the APC gene, which is believed to be a tumour suppressor gene. The coding portion of the gene contains 8538 base pairs and gives rise to an approximately 300kd protein with 2843 amino acids. The recent sequencing of the APC gene has made direct mutation analysis possible.[7-9] In several studies the area of APC gene mutation correlates to the number of appearing polyps.[10] Men and women are affected equally. One third of the newly diagnosed cases represent new mutations (Table 2).

The goal of the study of Wu et al.[11] was to identify various APC gene types with the FAP phenotype in order to recognize specific mutations correlating with severe polyposis. The postoperative course was analyzed in 58 patients from 19 FAP families with evidence of an APC gene mutation. The severity of the FAP was defined using the number of polyps(<1000 mild,>1000 severe). In all patients, 8 different APC mutations were identified. Mutations on codons 1309 and 1328 in exon 15G were associated with a severe polyposis phenotype. These patients underwent proctectomy more frequently. Of the 43 patient who initially received an ileorectal anastomosis or a partial colonic resection, the rectum later had to be removed in eight. Seven of these 8 had a mutation on codon 1309 or 1328.The rectum was preserved in all other patients, with one exception, when the mutation was outside the area of codon 1309 or 1328. The results of this study show that a precise analysis of the germline mutations can play an important role in surgical decision-making and planning.

Turcot syndrome is due to mutations in either the APC gene or in the mismatch repair genes MLH1 (OMIM#120436) or PMS2 (OMIM#600259). Germ line molecular alterations in the TPS3 gene have not been observed. Turcot's syndrome of glioma and polyposis occurs in the absence of germ line mutations of exons 5 to 9 of the p53 gene.[12]

Various molecular studies in search of the susceptibility locus for P-J. S have indicated three independent loci on chromosomes 1p, 6 (pericentromeric region) and 19p (OMIM#175200).[13]

Most authors consider Turcot syndrome, familial adenomatous polyposis and Gardner syndrome to be common entities representing a variable phenotypic expression of a single autosomal dominant genetic disorder.[14]

3.CONGENITAL HYPERTROPHY OF THE RETINAL PIGMENT EPITHELIUM (CHRPE) IN INHERITED POLYPOSIS SYNDROMES

a. CHRPE in the general population

Congenital Hypertrophy of the Retinal Pigment Epithelium (CHRPE) was first reported in the benign melanoma of the retinal pigment epithelium.However, CHRPE is also found in the normal population. It is characterized clinically as an isolated, well-delineated, flat, pigmented lesion at the level of the retinal pigment epithelium. The lesions range from less than 0.1 to greater than 14 disc diameter (DD) in size. The pigmentation may be variable and there may be depigmented lacunae and a hypopigmented halo. They are believed to occur rarely in individuals and, when present, are usually solitary and unilateral.

Solitary CHRPE as well as congenital grouped pigmentation differ clinically from the multiple pigmented lesions seen in familial adenomatous polyposis (FAP) and patients with these conditions as well as their relatives, are not at a greater risk of developing intestinal cancer. The only possible exception was a child with bilateral sporadic retinoblastoma and bilateral congenital grouped pigmentation who had three older relatives with colonic cancer.[15]

Lewis and Traboulsi assessed the frequency of the retinal pigmentation in the general population. Lewis reported the incidence of bilateral pigmentation as 0.1 per cent and Traboulsi reported 4.8 per cent bilateral pigmentation and 33,3 percent pigmentation in 42 control cases.[16] In another series no bilateral pigmentation was observed in 1984 normal individuals of whom 6 had unilateral pigmentation (0.3 percent). The incidence was reported to be much lower in the Japanese population.

Apart from in the general population, CHRPE has been reported in association with inherited polyposis syndromes and the presence of multiple CHRPE lesions has been correlated with the presence and development of polyposis in these conditions.[14]

Despite the absence of histopathologic proof, the pigmented ocular lesions of familial adenomatous polyposis have been termed congenital hypertrophy of the retinal pigment epithelium by several authors, because of the ophtalmoscopic similarity to isolated patches of congenital hypertrophy of the retinal pigment epithelium found in normal individuals.

Both solitary CHRPE and its multifocal variant called congenital grouped pigmentation are well known to

Table 2. Clinical characteristics and ocular findings in the inherited gastrointestinal polyposis syndromes and of hereditary non-polyposis colorectal cancer (adopted from references 2 and 3) AD=Autosomal dominant, AR=Autosomal residual CHRPE=congenital hypertrophy of the retinal pigment epithelium

Adenomatous Polyposis Syndromes	Gasrointestinal Lesions	Extraintestinal Lesions	Ocular Findings	Predisposition to Cancer
Familial Adenomatous Polyposis (AD) OMIM=175100	Multiple(>100) Gastrointestinal Polyps mainly In colon and rectum	None	CHRPE	Colon adenocarcinoma In all untreated patients
Gardner syndrome (AD) OMIM=175100, 276300	Same as familial adenomatous polyposis	Osteomas of the skull and mandible, epidermoid & dentigerous cysts, lipomas, fibromas, and desmoid tumours	CHRPE	Colon adenocarcinoma in all untreated patients, other cancers also reported (e.g., thyroid liver, brain)
Turcot's syndrome (Considered AD by most authors, AR byothers) OMIM=276300	Same as Familial Adenomatous Polyposis	Neuroepithelial brain tumours (meduloblastoma, glioblastoma)	CHRPE, signs of intracranial tumour	Colon adenocarcinoma, Ileal reticulum Cell sarcoma, &Thyroid papillary carcinoma have been reported in association.
Hamartomatous Polyposis Syndromes				
Peutz-Jeghers syndrome (AD) OMIM=175200	Multiple (few to hundreds) gastrointestinal polyps, most frequently in small bowel	Melanin spots on lips, buccal mucosa, and digits.Hamartomas of other mucosal surfaces (nose, esophagus,bronchus)	Pigmentation of lips and conjuctiva	Gastrointestinal tract and other cancers in up to 48% of cases
Familial Juvenile Polyposis (AD) OMIM=174900	Multiple gastrointestinal polyps, most frequently in colon and rectum	None	None	Probable, but magnitude of risk unknown
Hereditary Nonpolyposis Colorectal Cancer* OMIM=114500	AD Adenomatous (few)	Rare osteomas	CHRPE negative	Colon cancer only in Lynch Type I; Endometrial cancer and colon cancer in Lynch Type II

*More than one loci are involved.

ophthalmologists. Traditionally these lesions have been considered to have little clinical significance. However many authors reported on the relationship of pigmented fundus lesions to FAP and Gardner syndrome and have frequently used the term CHRPE to describe these pigmented lesions. This is perhaps unfortunate because

many ophthalmologists are wondering whether the solitary or multifocal variants of CHRPE, which are commonly observed, may also be an indicator of FAP or Gardner syndrome. It has been suggested that patients with these isolated ocular conditions should be advised that their chances of developing cancer of the colorectal region are possibly no greater than the general population. Conversely, patients with characteristic bilateral, multiple, haphazardly arranged pigmented fundus lesions, and their relatives, should be evaluated for these potentially lethal colorectal tumours.[15]

b. The value of screening for CHRPE in FAP

The relationship between FAP and CHRPE was first reported by Llopis and Menero[17]; they found CHRPE in 10 patients and 3 possible carriers.

In FAP families it is important to identify definite possible carriers and no carriers by sublinical markers before polyposis develops. Expression of CHRPE varies from 100 to 83% in affected cases and from 0 to 43% in patients without FAP. Five of six studies had found multiple bilateral lesions to be highly specific markers (specificity 99-100%). Surprisingly, one series found bilateral lesions in four of 26 controls without FAP. However, when present, CHRPE is a reliable clinical marker for FAP in CHRPE-positive families. In CHRPE-negative families, negative ophthalmic examinations are of no diagnostic value.

CHRPE in familial adenomatous polyposis (FAP) patients appears as multiple bilateral lesions, the majority of which are less than 0.5 DD in size. A positive criterion for FAP was defined as the presence of at least four lesions whatever their size, or at least two lesions, one of which is large. This criterion showed a high sensitivity (0.68) and a maximal specificity (1). Within each family, the retinal phenotypic expressions was homogenous according to one study.[18] The term congenital hypertrophy of the retinal pigment epithelium was given to these lesions although no histologic proof was available. The histologic findings of the lesions are consistent with CHRPE, hyperplasia of the retinal pigment epithelium (RPE) and hamartomas of the RPE; other previous histopathologic reports also noted hypertrophy of the RPE along with a lesion consistent with a choristoma.

Several histological studies have stated that these lesions were hamartomatous lesions of retinal pigment epithelium, in which the hypertrophied cells are arranged in several layers, associated with an increase in number and size of melanin granules, a thickening of Bruch's membrane, and an alteration of the subjacent photoreceptors. A single or

atypical lesion may be difficult to differentiate from a choriodal melanoma or naevus, a chorioretinal scar from toxoplasma, or a secondary hyperplasia of the RPE. However the clinical picture and the family history should make the diagnosis clear.[18]

Adenomatous polyps usually develop around puberty and before 30 years of age although polyps have been diagnosed in patients as young as 12 months of age and as old as 80 years of age. A study of 153 members of 56 kind groups with FAP showed an average age for the development of polyps in patients with positive eye lesion to be 22.5 years. This study of 153 patients did not show any correlation between extracolonic manifestations and the CHRPE biomarker. Patients who were kin with CHRPE biomarker developed polyps at a significantly earlier age than did patients who were kind and did not have CHRPE lesions. In one study the average age of the 8 patients who developed polyps was 14.5 years.

In another study[19] only 50% of the patients who developed polyps had extra colonic manifestations, which consisted of epidermoid cysts. In these kind all patients with adenomatous polyps had at least 4 RPE lesions with a mean of 23 lesions. Thus, it appears that RPE lesions are far more sensitive in predicting the development of polyps than other extracolonic mani-festations. The vast majority of these lesions were less than 0.5 disc diameters in size.[20] CHRPE has been related to generalized expression of an abnormal gene in RPE but its functional abnormalities tend to be localized. Previous histopathologic studies of pigmented fundus lesions in patients with FAP have shown a diffuse abnormality of melanin pigment granules. The clinical, psychophysical, electrophysiologic and fluorescein angiographic findings in CHRPE in subjects with FAP were assessed in a study.[21] All subjects showed a mild hyperopia, on perimetry there were scotomas corresponding to some lesions. ERG showed normal rod, maximal, single–flash cone, and flicker responses. Fluorescein angiography demonstrated normal retinal vasculature overlying the CHRPE lesions.

The results suggest that although multiple CHRPE associated with FAP have been related to the widespread expression of the abnormal gene in the RPE cells, the functional abnormalities of such epithelium and overlying photoreceptors tend to be localized.[21]

c. CHRPE in Gardner's syndrome

The development of extracolonic malignancies (ECM) in FAP has, since 1953, been termed Gardner's syndrome.[22-23] Multiple patches of congenital hypertrophy of the retinal pigment epithelium (CHRPE) have

recentlty been described in a large number of kind with Gardner's syndrome; they are specific and sensitive clinical markers of this disease (specificity 0,952 and sensitivity 0,780).[24]

Lewis et al found CHRPE in 18 patients with Gardner's syndrome.[25] Thereafter Traboulsi et al[16] investigated 134 members of 16 family trees with Gardner's syndrome and found CHRPE in 37 of 41 patients (90.2 per cent).

The eyes of a 51-year-old woman with familial athenomatous polyposis and extra colonic manifestations (Gardner's syndrome) which were obtained postmortem and studied by light microscopy and by transmission and scanning electron microscopy[24] showed a generalized abnormality in melanogenesis of the retinal pigment epithelium and at least three types of pigmented lesions. The histologic findings in one type of lesion were consistent with congenital hypertrophy of the retinal pigment epithelium featuring cellular hypertrophy hyperplasia and, rarely, retinal invasion and formation of a minute mushroom-shaped tumour. It is important to mention that the weight of clinical and genetic evidence now suggests that there is no distinction between Gardner's syndrome and FAP as clinical entities as well as genetic entities and they are both due to mutations of the APC gene.[17]

d. CHRPE in Turcot's syndrome

In 1959 Turcot and colleagues reported two siblings with polyposis of the colon and central nervous system tumours.[26] This association has subsequently become known as Turcot syndrome or the glioma-polyposis syndrome. This is a rare condition: fewer than 60 cases have been reported worldwide, and only 34 of them had histopathologic confirmation of the diagnosis. Turcot syndrome is a hereditary condition characterized by multiple, adenomatous gastrointestinal polyps associated with neuroepithelial tumours of the central nervous system. Children and young adults with multiple patches of CHRPE and a family history of adenomatous polyposis may be at increased risk for the development of central nervous system tumours as well as gastrointestinal polyps. In Turcot's syndrome, neural tumours (e.g. glioma or meduloblastoma) associated with FAP normally develop at a very young age, often before the onset of the polyps and are a good marker for the disease if the parent is already known as an FAP patient. The value of this ECM as a predictive marker in the FAP population is limited by the very low prevalence of Turcot's syndrome reported.

e. CHRPE in Peutz-Jeagers syndrome

The abnormal pigmentation in Peutz-Jeghers syndrome (P-J. s) usually appears in infancy or early childhood on the lips, digits, and buccal mucosa.[12,27] It is also occasionally seen in the intestinal mucosa.

Fewer than 5% of P-J. syndrome patients have no abnormal pigmentation and less than 5% of patients with such pigmentation have no polyps. In this syndrome the abnormal eye pigmentation is periocular and melanotic spots are seen along the eyelid margins, over the eyelid skin and, less frequently, on the palpebral conjunctiva.

4. THE CONTRIBUTION OF OPTHALMOLOGIC SCREENING IN THE SURVEILLANCE OF INHERITED POLYPOSIS SYNDROMES

Abnormalities of the retina were first described in association with FAP in 1935 but it was not until 1980 that the potential for CHRPE as a marker of the disease was recognized. Initially it was believed that CHRPE was associated only with Gardner's syndrome. Subsequent studies from the USA, Japan and the UK have shown CHRPE to be present in a high proportion of FAP family members (65-100%) with and without ECM of Gardner's syndrome.[28]

CHRPE was subclassified by appearance into two or four different types of lesions.[24] Pigmentations, when classified into two types, as Traboulsi et al reported, are named large and small pigmentations. The large pigmentations are distributed close to the posterior pole and are 0.5 to 2 times papillary diameter in size. Some large pigmentation is accompanied by peripheral marginal halo. The large pigmentation is shaped like a watermelon or persimmon seed. The small pigmentation is distributed in the peripheral zone and is black in colour. Among patients and possible carriers, there is no difference in the number of large pigmentations shown; however the number of small pigmentations is greater in patients; 5.0 average in patients and 1.7 average in possible carriers. The number of small pigmentations may increase as the disease progresses.

The four types classification of pigmentation includes: type a (oval pigmented with halo), type b (small round pigmented dots), type c (large round pigmented dots) and type d (round depigmented dots). A study suggested that type b lesions may proliferate with age.[19] There seems to be an intrafamilial consistency in the number of fundus lesions in affected individuals, although in some families

affected individuals may have no any lesions. A total number of four or more lesions in one or both eyes is generally accepted as indicative of the ocular trait. A recent study of children at risk for Gardner's syndrome has shown that, over a follow-up period of up to four years, only those who had fundus lesions developed colonic polyps. Although about 20% of patients with familial adenomatous polyposis syndromes do not have fundus lesions, the absence of the ocular trait should not be taken as evidence of absence of the disease.

In a FAP family with CHRPE, an at-risk person negative for CHRPE has a reduced risk of carrying the defective gene. However, the only test, which is 100% certain to exclude an individual from carrying the gene, is mutational analysis.[29-30]

In the largest study to date in which the association of RPE lesions with FAP was examined it was reported that two thirds of kind with FAP have RPE lesions. In these kind, all patients with diagnosed polyps had at least four RPE lesions. Thus, the presence of 4 or more total RPE lesions is considered significant as a biomarker for the presence of polyps and all patients with 4 or more RPE lesions whatever their size, or at least 2 lesions of which one is large constitutes the best diagnostic criterion of the examination of fundus in patients affected by FAP. These patients should undergo annual sigmoidoscopic examinations beginning before 10 years of age.[17]

A number of authors have confirmed the high specificity (close to 1) of these retinal lesions but with a lower and more variable sensitivity (between 0.6 and 0.8). Until now no hypothesis has been proposed to explain the absence of retinal lesions in 20-40% of the FAP patients.

Although most adenomatous polyposis coli gene carriers have such epithelial hypertrophy, there is interfamilial variation. There is good evidence that short and very long mutant proteins are indeed unstable but variations in the stability of different truncated proteins within the CHRPE - associated region have not yet been studied.[31] In families in which known adenomatous polyposis coli gene carriers are CHRPE-negative, the absence of CHRPE in at-risk relatives cannot be used to modify risk[32] although there seems to be a negative correlation between CHRPE and desmoid tumours.[33]

5. GENETICS AND CHRPE IN INHERITED ADENOMATOUS POLYPOSIS SYNDROMES

The gene responsible for FAP, called the adenomatous polyposis coli (APC) gene, is localized to the long arm of chromosome 5(5q21-q22) and was identified in 1987[34] and cloned in 1991.[10,35] A number of different mutations of this gene have been found to cause FAP.[8,36] There are methods which detect the most frequent mutations in the gene. Direct detection of the various mutations is not generally indicated because it is very laborious and time consuming[37]. In the APC gene responsible for FAP, more than 250 different mutations have been described.[31] Cluster region in exon 15, occurs in about 20% of the patients with FAP. Verifying a mutation in the FAP gene of a representative index patient yields a 100% reliability for all first-degree at-risk persons. An indirect gene analysis with DNA-linked markers to identify the segregation phase of the FAP gene can also be used in the clinical diagnosis of FAP, but at least two affected members of one family are required for examination. However, there are patients in whom the risk of developing the disease cannot be estimated by either of the two genetic analyses. A possible alternative is the detection of a shortened protein product in a known target sequence.[9] The results of the molecular genetic analyses correspond with those of ophthalmic examinations; that is both indicate a high probability for development of FAP manifestations in the at-risk persons with CHRPE.

The presence of CHRPE is dependent on the position of the mutation along the coding sequence of the FAP gene. Opthalmoscopy facilitates genetic analysis of the APC gene mutations, thus the combination of an ophthalmic examination with a DNA analysis and endoscopy improves the risk assessment for polyposis syndromes carriers.[37] The variation between family members and between the two eyes of a single individual presumably indicates that the development of CHRPE is not solely dependent on the underlying constitutional mutation but on a second somatic event in the retinal pigment epithelial cells, like many of the other extracolonic manifestations of inherited polyposis disease.[29-30]

The retinal lesions are only present if the mutation is located between codons 463 and 1387 of the APC gene. Specifically, mutation de novo can be detected more easily when the retinal phenotype is known. The important heterogeneity between families and the homogeneity within families of the retinal phenotype are explained by the situation of constitutional mutations of the APC gene in each family.

The latest genetic studies have demonstrated that

CHRPE expression depends on the length of abnormal protein produced by the defective APC gene.[18-19]

Lesions of congenital hypertrophy of the retinal pigment epithelium are almost always absent when the mutation occurs before exon 9, with the exception of patients with mutations between codons 1445 and 1578. They are almost always present when the mutation occurs after exon 9. However, mutations in exon 9 can result in either a CHRPE-positive or-negative individual within the same family (Table 3).

Thus the status of CHRPE considerably facilitates locating the mutation in genetic diagnosis and permits a more efficient search for the mutation. There is evidence that, in patients with the mutation at exon 15, the clinical course of the disease is more aggressive and the onset of FAP is earlier, compared to persons with mutations in other locations. This observation is important for the management of patients with FAP.[37-38] Moreover, the correlation between the location of the mutation in the APC gene and the CHRPE status of an individual is known to be closely associated with the position of the mutation site. Patients with mutations between codons 312 and 1444 are CHRPE-positive, whilst mutations in other sites result in a CHRPE negative phenotype.[33]

Mutational analysis of the APC gene, although expensive and time-consuming, will hopefully provide the most valuable tool for screening.[29] The CHRPE status of an individual provides a genotype to phenotype correlation, which should allow a more rapid genetic confirmation of suspected FAP, in future patients. The CHRPE status provides a guidance to the likely position

of the causative mutation and thereby an indication of the potential severity of disease (Table 4). In families with known CHRPE stigma, all members need regular gastrointestinal investigations.[31]

6. Screening and follow up programmes for inherited polyposis syndromes

FAP is a condition that, when left untreated, leads inevitably to the development of colorectal carcinoma. Although the spontaneous mutation rate has been estimated as up to 40 per cent, colorectal carcinoma should be entirely preventable in at least 60 per cent of

Table 3. The APC gene mutations, CHRPE status, age when polyps were first seen and the number of polyps for each affected individual (adopted from reference 14)

Mutation site	CHRPE status	Age polyposis first seen (years)	No of polyps
Exon 4	Negative	31	100$_s$
Exon 7	Negative	29	100$_s$
Exon 9	Negative	43	80+
Exon 15A	Positive	42	1000+
Exon 15A	Positive	15	100+
Exon 15B	Positive	28	1000+
Exon 15C	Positive	53	100$_s$
Exon 15E	Positive	37	100$_s$
Exon 15E	Positive	25	250+
Exon 15F	Positive	26	100+
Exon 15F	Positive	28	1000+
Exon 15G	Positive	15	1000+

Table 4. Findings from 6 studies of CHRPE in known affected individuals with and without adenomatous polyposis. Numbers in parenthesis are numbers of individuals in non-FAP group (adopted from reference 11).

			% of cases with CHRPE			
		with FAP			*without FAP*	
Study	**No of families**	**No of cases**	**Total**	**Bilateral**	**Total**	**Bilateral**
Traboulsi et al.Baltimore Maryland, USA	16	41	90	78	33(42)	5
Berk et al.Toronto, Canada	9	40	87.5	-	0(8)	-
Baba et al.Hamamatsu, Japan	15	23	83	65	0.03 (1984)	0
Chapman et al. Newcastle, UK	25	40	100	-	43(35)	-
Polkinghorne et al. London, UK	-	72	97	90	30(26)	15
Morton DG Birmingham, UK	20	32	84	81	50(10)	0

cases, through effective family screening. All affected family members will go on to develop colorectal carcinoma, usually by the age of 35-40 years. Because the age at which colorectal polyps develop varies, screening by repeated bowel examination is necessary from puberty until at least 40 years of age before a family member can be considered unaffected.[7,19] In FAP the earliest recognition of cancer reported in Japan is in a three-year-old female infant.[17] The justification for screening as a method of cancer prevention in inherited adenomatous polyposis syndromes (IAPS) is well established. The cancer risk in IAPS patients presenting with symptoms varies from 32%-57%. Ophthalmic examinations and molecular genetic analyses have been established as noninvasive methods for determining the risk for a carrier of familial adenomatous polyposis syndromes.

FAP has a reported incidence of 0,4-1,3 per 10.000 and a point prevalence of about 1 per 35.000. The most complete data come from Scandinavia where population-based registers have been established for more than a decade. In clinical practice more data about the population frequency of the diagnostic criteria used for CHRPE and the concordance rate within families are needed before any further modification of risk using interfamilial observations can be used. To date neither reference gives sufficient data from population findings or degrees to permit intra-familiar concordance rates to be calculated.[39] Genetic testing for DNA obtained from peripheral blood samples is available and can test DNA linkage markers to the APC gene. The use of linkage markers requires that two family members already have a firm diagnosis of FAP. Such markers can diagnose more than 95% of persons at risk of FAP with greater than 98% accuracy. A method for detection of abnormal APC protein is available and can detect up to 87% of gene carriers. Direct detection of APC gene mutations is not yet practical because most FAP families have unique APC mutations, although a few mutations have been found to be common to a number of families. Genetic test should be first performed at 10-12 years of age. If positive the follow up should be as previously described. If negative sigmoidoscopic should be performed every 3-5 years until 40 years of age. The predictive value of indirect genotype analyses reached 83.3% risk estimation, and, with regard to the carrier status, direct mutation analyses allow risk estimation in 50% of patients.

Testing of children younger than 10 years of age should be avoided because it is not clinically important and may lead to problems with parental bonding, peer rejection and poor self-image.

A simple means of identifying at least 80% of gene carriers is the detection of multiple areas of CHRPE by indirect fundoscopy. The presence of at least four small fundus lesions or one large lesion indicates a carrier status of FAP. Patients with characteristic bilateral multiple fundus lesions should be evaluated for colorectal tumours.[37] These results can be combined by standard genetic risk calculation using Baye's theorem, to give a more precise estimate of the risk of carrier status.[39]

Early reports have suggested that there are many different mutations spread throughout the gene, which would make identification of each lesion difficult and possibly unfeasible as a screening measure.[40-41]

The identification of CHRPE is more widely informative than linked polymorphic markers because it can also be applied to smaller pedigrees.[7] It has been supported that small pigmentation appears to increase in number around the age of the appearance of the polyps.[19] Traboulsi et al[4] observed small pigmentation distributed in the peripheral zone and large pigmentation distributed close to the posterior pole. Thus the small pigmentation appears to increase in number or to become recognizable around the age of the appearance of the polyp. The generalized disturbance of melanogenesis and the formation of spherical melanin granules in the retinal pigment epithelium of these patients with adenomatous polyposis needs further investigation.

Family members whose fundi have been examined and found to be devoid of CHRPE have a reduced risk of carrying the defective gene and, therefore, of developing polyps. Considerable reassurance can be gained from this; however the only test, which is 100% certain to exclude an individual from carrying the gene, is mutation analysis.[31] Upper gastrointestinal screening should begin when the diagnosis of colonic polyposis is made (every 1-3 years).Especially in FAP patients, special attention must be paid to regular screening for carcinoma in the ampulla of Vater. Small bowel radiography should be performed in those found to have prominent duodenal polyps if the patient is to have surgery.

A major problem in many studies that might possibly affect conclusions is the diagnosis of individuals (and not families) as having familial adenomatous polyposis (FAP) without extracolonic manifestations (ECM) as opposed to FAP with ECM or Gardner's syndrome. As is the case with most multi-system dominant syndromes, variable expressivities are the rule (Table 5). Within families with

Gardner's syndrome, many patients with polyposis will not show ECM, except for possibly the ocular lesions or the jaw lesions, which are probably the most common. When we label pedigrees of families as Gardner's syndrome because at least one member of each family had ECM other than congenital hypertrophy of the retinal pigment epithelium (CHRPE), we must be skeptical. In those families some affected individuals may have polyposis and CHRPE but no other ECM; those individuals should also be considered to have Gardner's syndrome. The absence of CHRPE in individuals at risk for adenomatous polyposis cannot preclude regular colonic screening, and this dictum should be followed up in the management of all families. All groups studying the genetics and extracolonic manifestations of adenomatous polyposis should use family diagnosis and not individual diagnosis as a basis for labelling patients with inherited polyposis syndromes. On the other hand it is strongly supported that anachronistic labelling of affected families complicates individual management and long-term screening to map out the unknown spectrum of extracolonic manifestations occurring in any combination in any one patient. Some of the updated results support the consistent finding of ocular lesions, which are not more pathognomonic in patients with or without other extracolonic manife-stations.[1-2] Results argue for a combined screening program for FAP of DNA analysis indirect opthalmo-scopy and bowel examination[7,20,32] (Table 6). Unlike repeated bowel screening both of these tests can be performed at a single hospital visit and their accuracy of predictive diagnosis can be improved by combined risk analysis[7]. In these series the youngest affected patient examined was 13 months old.[18]

Any regional registry can provide an effective screening and counseling service to gastroenterologists and surgeons treating patients with FAP.[42] For example it can be estimated that a 15 year old first degree relative with a negative sigmoidoscopy has a 30 per cent chance of carrying the affected gene but, a 30 year old first degree relative without detectable colorectal adeno-matous polyps has a less than 1 in 10 chance of being affected.[39]

Cancer is almost never present at the time of polyposis diagnosis in patients who undergo interval prospective screening. Screening of FAP should be done by video or fiber optic endoscopy because of the usually small size of the polyps and the requirement of histology for diagnosis. Children of affected patients should undergo flexible proctosigmoidoscopy beginning at 10 to 12 years of age and continuing every 1 or 2 years until 35 years of age; thereafter examinations should be performed every 3 years. Adenomas of the colon and rectum are common, with an extremely high incidence (up to 100%) of malignant transformation. Fundic gland polyps of the stomach and adenomas of the small intestine also occur. The study of Strater et al.[43] showed that adenomatous transformation of colon epithelium is associated with a considerable increase of the cellular turnover rate and with a severe disturbance of the microtopographical localisation of birth and death of enterocytes.

Although extracolonic neoplastic change is most common in tissues and organs of mesenchymal-tissue derivation, it is by no means limited to them. A suggestion that a wide variety of epithelial tumours arising in primary anatomic sites outside the colon might be caused by a single mutant gene that also produces FAP was first made in 1969.[44] A vast variety of other neoplastic changes (not involving thyroid, brain, or connective tissue) have been reported to occur with IAPS. A few of the more interesting of these changes include pigmented nevi, malignant melanoma, periampullary malignancy, adenomatous and juvenile polyposis of the stomach and small intestine, multiple endocrine adenomatosis, endometrial carcinoma, prostatic carcinoma, papillary

Table 5. Special characteristics of the inherited polyposis syndromes

1. Delayed age of onset

2. Pleiotropism (multiple effects of single gene)

3. Variable expressivities (qualitative-quantitative mani-festations)

4. Penetrance (variable expressivity)

5. Genetic heterogeneity (different mutations=same pheno-type)

Adopted from T.Yamada Textbook of Gastroenterology (vol 2) page 1945

Table 6. Screening methods in inherited polyposis syndromes

1. *Non-invasive screening methods*

   -Family tree

   -Clinical examination for ECM

   -Dilated fundus examination (CHRPE)

   -DNA analysis

   -APC gene mutations

2. *Invasive screening methods*

   -endoscopy

   -small bowel radiography

   -fundus angiography

bladder tumour, and chromophobe adenoma. In many instances available evidence suggests that these changes are phenotypes of the same mutant gene that produces FAP.[45-49] Any patient with FAP must be considered at risk for a wide variety of serious malignancies. Since neoplasms are commonly metachronous in onset, careful lifelong medical observation is indicated. In addition, selected patients with papillary carcinoma of the thyroid or brain tumours should be evaluated for FAP.[44]

The malignant potential of the adenomatous polyps that develop in patients with FAP is 100%. The average interval between the discovery of polyps and the appearance of symptoms is 10 years. In patients who are symptomatic from the polyps, two thirds already have carcinoma of the colon or rectum. Once polyps are diagnosed in patients with FAP, a prophylactic colectomy is recommended.[20] Basically, there are two surgical options for FAP patients - subtotal colectomy with ileorectostomy on the one hand or total colectomy with pouch-anal anastomosis or terminal ileostomy on the other. The first option leaves a residual rectum with the sometimes not inconsiderable risk of carcinoma developing in the preserved rectum.

It is believed that all the pigmented ocular lesions in familial adenomatous polyposis syndromes, even those that are one cell layer in thickness, represent hamartomas of the retinal pigment epithelium. The ocular lesions in familial adenomatous polyposis probably develop because of the effect of the abnormal gene responsible for the formation of other benign and malignant tumours. The cells in these tumours have abnormal metabolic functions and produce large and abnormal melanin granules that distend the cells. We do not know whether all these processes occur before birth or early in life, or whether such lesions continue to grow and change throughout life. Although congenital hypertrophy of the retinal pigment epithelium is generally believed to be a stable non-progressive lesion, rare cases with photographically documented enlargement have been reported.[50-52] Familial adenomatosis polyposis with extracolonic manifestations could probably best be classified as a phakomatosis because it is dominantly inherited, has abnormalities and tumours involving tissues derived from all three embryonal layers, and has a strong predispo-sition for the development of cancer.

7. CONCLUSIONS

Increased patient longevity is teaching us about the generalized nature of inherited adenomatous polyposis

syndromes (IAPS) as a pluripotential genetic defect no restricted to the colorectum. When present, CHRPE lesions are a reliable clinical marker for IAPS in CHRPE-positive families.[47-52] In CHRPE-negative families, negative ophthalmic examinations are of no predictive value. The combination of an ophthalmic examination with clinical examination, DNA analysis and endoscopy improves the risk assessment of inherited adenomatous polyposis syndromes carriers.

REFERENCES

1. Traboulsi EI. Familial adenomatous polyposis. Dis Col Rectum 1989; 32: 633-4
2. Cohen Z, Mc Leod RS, Berk Th. Familial adenomatous polyposis. Dis Col Rectum 1989; 32: 634
3. Maher EP, Moore AT. Congenital hypertrophy of retinal pigment epithelium and risk estimation in adenomatous polyposis coli. Lancet 1990; 335:791
4. Traboulsi EI, Maumenee IH, Krush AJ, Giardiello FM, Levin LS, Hamilton SR. Pigmented ocular fundus lesions in the inherited gastrointestinal polyposis syndromes and in hereditary nonpolyposis colorectal cancer. Ophthalmology 1988; 95: 964-969
5. Lynch HT, Smyrk TC, Watson P, Lanspa SJ, Lynch PM, Jenkins JX. Hereditary flat adenoma syndrome: a variant of familial adenomatous polyposis? Dis Colon Rectum 1992;35: 411-421
6. Burt RW. Polyps syndromes screening and diagnostic studies. In: Textbook of Gastroenterology (vol 2). T. Yamada (Ed), Lippincott 2nd edition Philadelphia 1995. 3d edition 1999, p.1995-2022
7. Morton DG, Gibson J, Macdonald F, et al. Role of congenital hypertrophy of the retinal pigment epithelium in the predictive diagnosis of familial adenomatous polyposis. Br J Surg 1992; 79: 689-693
8. Nishisho I, Nakamura Y, Myioshi Y, et al. Mutations of chromosomes 5q21 genes in FAP and colorectal cancer patients. Science 1991;253:665-9
9. Van der Luijt R, Khan PM, Vasen H, et al. Rapid detection of translation-terminating mutations of the adenomatous polyposis coli (APC) gene by direct protein truncation test. Genomics 1994;20:1-4
10. Kinsler KW, Nilbert MC, Su LK, et al. Identification of FAP locus genes from chromosome 5q21. Science 1991;253:661-5
11. Wu JS, Paul P, McGannon EA, Church JM.APC genotype, polyp number and surgical options in familial adenomatous polyposis. Ann Surg 1998; 227: 57-62.
12. Peutz JL. On a very remarkable case of familial polyposis of the mucous membrane of the intestinal tract and nasopharynx accompanied by peculiar pigmentations of the skin and mucous membrane. Nederl Maandschr Geneesk 1921;10:134
13. Jeghers H, McKusick VA, Katz KA. Generalized intestinal polyposis and melanin spots of the oral mucosa,

lips and digits. N Engl J Med 1949;241:993

14. Munden PM, Sobol WM, Weingeist TA. Ocular findings in Turcot syndrome (glioma-polyposis). Ophthalmology 1991; 98: 111-4

15. Shields JA, Shields CL, Shah PG, Pastore DJ, Imperiale SM. Lack of association among typical congenital hypertrophy of the retinal pigment epithelium, and Gardner syndrome. Ophthalmology 1992; 99:1709-1713

16. Traboulsi EI, Maumenee IH. Periocular pigmentation in the Peutz-Jeghers syndrome. Am J Ophthalmology 1986; 102: 126-127

17. Llopis MD, Menero JL. Congenital hypertrophy of the retinal pigment epithelium and familial polyposis of the colon. Am J Opthalmol 1987;103:235-6

18. Tiret A, Taiel-Satral M, Tiret E, Laroche L. Diagnostic value of fundus examination in familial adenomatous polyposis. Br J Ophthalmology 1997; 81: 755-758

19. Morton DG, Macdonald F, Haydon J, et al. Screening practices for familial adenomatous polyposis: the potential for regional registers. Br J Surg 1993; 80: 255-258

20. Romania A, Zakov ZN, Church JM, Jagelman DG. Retinal pigment epithelium lesions as a biomarker of disease in patients with familial adenomatous polyposis. A follow-up report. Ophthalmology 1992; 99 : 911-913

21. Santos A, Morales L, Hernandez-Quintela E, Jimenez-Sierra JM, Villalobos JJ, Panduro A. Congenital hypertrophy of the retinal pigment epithelium associated with familial adenomatous polyposis. Retina 1994;14:6-9

22. Gardner EJ, Stephens FE. Cancer of the lower digestive tract in one family group. Am J Hum Genet 1950;2:41.

23. Lynch HT, Priluck I, Fitzsimmons ML. Congenital hypertrophy of retinal pigment epithelium in non-Gardner's polyposis kindred's. Lancet 1987; 2 (8554): 333

24. Traboulsi EI, Murphy SF, Dela Cruz Z, Maumenee IH, Green WR. A clinicopathologic study of the eyes in familial adenomatous polyposis with extracolonic manifestations (Gardner's syndrome). Am J Ophthalmology 1990; 110: 550-561

25. Lewis RA, Crowder WE, Elerman LA, Nussbaum RI, Ferrel RE. The Gardner syndrome: significance of ocular features. Opthalmology 1984;91:916-25

26. Turcot J, Despres J-P, St Pierre F. Malignant tumours of the central nervous system associated with familial polyposis of the colon. Dis Colon Rectum 1959;2:465-8

27. Heyen F, Jagelman DG, Romania A, et al. Predictive value of congenital hypertrophy of the retinal pigment epithelium as a clinical marker for familial adenomatous polyposis. Dis Colon Rectum 1990; 33 : 1003-1008

28. Gardner EJ, Richards RC. Multiple cutaneous and subcutaneous lesions occurring simultaneously with hereditary polyposis and osteomatosis. Am J Hum Genet 1953;5:139-147

29. Hickey-Dwyer MU, Willoughby CE. Assessment of the value of congenital hypertrophy of the retinal pigment epithelium as an ocular marker for familial adenomatous polyposis. Eye 1993; 12:562-4

30. Reck AC, Bunyan D, Eclles D, Humphrey R.The presence of congenital hypertrophy of the retinal pigment epithelium in a subgroup of patients with adenomatous polyposis coli mutations. Eye 1997;11:298-300

31. Reck AC, Bunyan D, Eccles D, Humphry R. The presence of congenital hypertrophy of the retinal pigment epithelium in a subgroup of patients with adenomatous polyposis coli mutations. Eye 1997; 11:298-300

32. Houlston RS, Slack J, Murday V. Congenital hypertrophy of retinal pigment epithelium and risk estimation in adenomatous polyposis coli. Lancet 1990 ; 335:791

33. Caspari R, Olschwang S, Friedl W, et al. Familial adenomatous polyposis: desmoid tumours and lack of ophthalmic lesions (CHRPE) associated with APC mutations beyond codon 1444. Hum Mol Genet 1995;4:337-40

34. Bodmer WF, Bailey LJ, Bodmer J, et al. Localization of the gene for familial adenomatous polyposis on chromosome 5. Nature 1987;328:614-619

35. Traboulsi EI, Krush AJ, Gardner EI, et al. Prevalence and importance of ocular fundus lesions in Gardner's syndrome. N Engl J Med 1987;316:661

36. Burt RW, Groden J. The genetic and molecular diagnosis of adenomatous polyposis coli. Gastroenterology 1993;104:1211-1214

37. Ruhswurm I, Zehetmayer M, Dejaco Cl, Wolf B, Karner-Hanusch J. Ophthalmic and genetic screening in pedigrees with familial adenomatous polyposis. Am J Ophthalmology 1988; 125: 680-686

38. Bunyan DJ, Eccles D, Shea-Simonds J, Reck AC. Genotype-Phenotype correlations of novel causative APC gene mutations in patients with familial adenomatous polyposis. J Med Genet 1995;32:924-31

39. Rhodes M, Chapman PD, Burn J, Gunn A. Role of a regional register for familial adenomatous polyposis: experience in the Northern Region. Br J Surg 1991; 78: 451-452

40. Houlston R, Slack J, Murday V. Risk estimates for screening adenomatous polyposis coli. Lancet 1990;1:484

41. Giradello FM, Offerhaus GJ, Traboulsi EI, et al. Value of combined phenotypic markers in identifying inheritance of familial adenomatous polyposis. Gut 1991;32:1170-1185

42. Burn J, Chapman P, Delhart J, et al. The UK Northern Region genetic register for familial adenomatous polyposis coli: use of age of onset, congenital hypertrophy of the retinal pigment epithelium and DNA markers in risk calculations. J Med Genet 1991;28:289-96

43. Strater J, Koretz K,Gunthert AR, Moller P. In situ detection of enterocytic apoptosis in normal colonic mucosa and in familial adenomatous polyposis. Gut 1995;37:819-825

44. Smith WG, Kern BB, The nature of the mutation in familial multiple polyposis: papillary carcinoma of the thyroid, brain tumours and familial multiple polyposis. Dis Col Rectum 1973; 16: 264-271

45. Leppert M, Dobbs M, Scambler P, et al. The gene for familial polyposis coli maps to the long arm of chromosome 5. Science 1987;238:1411-13

46. Meera-Khan P, Tops CM, van den Broek M, et al. Close

linkage of a highly polymorphic marker (D5S37) to familial adenomatous polyposis (FAP) localization on chromosome 5q21-q22. Hum Genet 1988;79:183-5

47. Rustin RB, Jagelman DS, McCannon, Fazio VW, Lavery IC, Weakley FL. Spontaneous mutation in familial adenomatous polyposis. Dis Colon Rectum 1990;33:52-5

48. Murday V, Slack J. Inherited disorders associated with colorectal cancer. Cancer Surv 1989; 8:139-57

49. Groden J, Thiveris A, Samovitz W, et al. Identification and characterization of the familial adenomatous polyposis coli gene. Cell 1991;66:589-600

50. Spigelman AD, Phillips R. Association of congenital hypertrophy of the retinal pigment epithelium with familial athenomatous polyposis. Br J Surg 1990; 77 : 1195

51. Iwama T. Association of congenital hypertrophy of the retinal pigment epithelium with familial adenomatous polyposis. Br J Surg 1990; 77 : 1195

52. Baker RH, Heineman MH, Miller HH, DeCosse JJ. Hyperpigmented lesions of the retinal pigment epithelium in familial adenomatous polyposis. Am J Med Genet 1988;31:427-435