Congenital hypertrophy of the retinal pigment epithelium (CHRPE) and familial adenomatous polyposis (FAP)

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ABSTRACT. Familial adenomatous polyposis (FAP) is a genetically transmitted disease affecting the colon. It is characterized by the presence of several (at least 100) adenomatous polyps, each able to develop into carcinomas, and by other extra-colonic signs such as skin and bone lesions. Within the framework of research studies to identify phenotypic markers for early detection of subjects at risk within a family affected by FAP, attention has recently been paid to congenital hypertrophy of the retinal pigment epithelium (CHRPE). With the aim of evaluating the relationship between FAP and CHRPE, 36 members of 7 FAP families were examined. We found that 43.75% of the subjects presenting CHRPE areas were also affected by FAP, whereas 58.33% of patients affected by FAP had CHRPE. Our findings indicated a lower incidence of CHRPE in FAP patients, compared to other studies reported so far. Moreover, in a control group of 160 healthy individuals we found a CHRPE prevalence of 5.5%.

Key words: familial adenomatous polyposis (FAP) - phenotypic marker - ocular symptoms - congenital hypertrophy of the retinal pigment epithelium (CHRPE).


Familial adenomatous polyposis (FAP) is a genetically determined disease affecting the colon and inherited as an autosomal dominant trait with a penetrance of 50-90%. The responsible gene is called APC (adenomatous polyposis coli), located at chromosome 5q21. The FAP frequency has been estimated to be approximately 1:8000 new-born babies, regardless of sex (Winaver 1985). FAP is characterized by the presence, at the colon level, of numerous adenomatous polyps, which are all potentially capable of developing into carcinomas; in addition, FAP may bring about several extra-colonic signs, specifically: intestinal (stomach and duodenum polyposis, carcinoma of Vater ampulla, gallbladder and bile duct carcinomas, hepatoblastoma), and extra-intestinal (desmoid tumors, osteomas, epidermoid cysts, thyroid carcinomas, multiple endocrine neoplasia, central nervous system tumors and congenital hypertrophy of the retinal pigment epithelium (CHRPE)). Many of the previously listed lesions may be found associated with well-known typical syndromes, i.e. Gardner syndrome (GS) and Turcot syndrome (TS).

Despite some earlier reports that considered GS, TS and FAP as manifestations of a single gene (Haggit & Reid 1986), more recently McKusick gave different reference numbers to the TS and FAP syndromes. Only GS and FAP are recognized to be allelic disorders (McKusick 1994).

When the diagnosis is made, at least 75% of symptomatic subjects also have a carcinoma of the colon and rectum; this explains why the early identification of the disease is essential in order to increase the patient life expectancy. Considering that a fully reliable biochemical or serum marker of this pathology is still not known, all patients at risk must be examined annually by rectum-sigmoid-colonoscopy from adolescence up to age 35 years, after which the probability of the development of colon polyps is significantly reduced (Bussey 1985; McKusick 1994). Within the framework of research studies carried out for the purpose of identifying phenotypic markers for early detection of subjects at risk within a family, specific attention has been paid to lesions of the retinal pigment epithelium (CHRPE).

These retinal anomalies were first reported by Blair & Trempe in 1980;
lesions were described as 'congenital, isolated, flat spots, with clear-cut margins, hyper-pigmented, located at the level of the retinal pigment epithelium, symptomless, round or oval, with free or focussed margins. In addition, there may be a hypo-pigmented halo surrounding the lesions' external margins as well as depigmented lacunae'. The overlying retinal vascularization may be altered. These lesions were found in three members of a family affected by Gardner syndrome which is now considered to derive from the same pleomorphic gene causing FAP. These authors stated that ophthalmoscopic examination can assist in the early identification of children at risk with regard to the development of FAP (Blair & Trempe 1980).

Since 1987 several studies have been made concerning the association of FAP with CHRPE and the capability of early identification in patients at risk of FAP, by examining the fundus oculi of subjects whose family group has already experienced this disease (Berk et al. 1988; Chapman et al. 1989; Diaz Llopis & Menezo 1987, 1988; Heyen et al. 1990; Iwama et al. 1990; Romania et al. 1989; Salvi et al. 1989; Traboulsi et al. 1987, 1988; Vadot et al. 1992).

Results
The pedigrees of our FAP families are shown in Fig. 1.

Our series of cases refers to 36 subjects (72 eyes) from 7 kindreds: 14 males (average age 26.42; min 10, max 44) and 22 females (average age 29.09; min 8, max 56). CHRPE areas have been found in 19 subjects, 7 males and 12 females; 3 of these 19 patients did not undergo colonoscopy owing to their age (3 girls: two are 8 years old and one is aged 9), therefore, it is not yet possible to ascertain if they have inherited FAP (Table 1).

We have also analyzed the prevalence of CHRPE in the 33 subjects studied from the gastroenterological standpoint. Twelve patients had FAP: 7 of these the search of CHRPE was positive (58.33%), while for 5 it was negative (41.66%). Within the 7 FAP and CHRPE positive subjects, 3 of them (2 females aged 24 and 25 years and 1 male aged 22 years) also presented further extra-colonic symptoms: osteomata of the jaw and skin fibromata. For this reason they have been considered as affected by Gardner syndrome. As regards the remaining 21 subjects who are not affected by Gardner syndrome, while for 12 the search was negative (57.14%). In addition, we also estimated the prevalence of FAP in sub-

Material and Methods
In order to evaluate the association of FAP with retinal pigment epithelium anomalies, we examined 36 at-risk members from 7 unrelated Italian FAP families. Prior to ophthalmologic examination 33 patients underwent a rectum-sigmoid-colonoscopy in order to ascertain or exclude the presence of intestinal lesions; in 3 patients this examination was not performed owing to their age (less than 10 years-old). We have considered affected FAP patients who had over 100 polyps. In all these subjects we have also investigated the presence of extra colonic features of FAP such as skin and bone alterations.

Ophthalmological assessment for CHRPE was performed blindly by two ophthalmologists, and when technically feasible photographs of the observed lesions were taken; one female patient was examined by means of fluorescein angiography to permit a more thorough study of the case; examination was made using Canon CF 60 U fundus camera. We considered those patients affected by CHRPE who had at least in one eye a lesion with the same characteristics described by Blair & Trempe (1980).

As regards 13 patients included in the first 4 families studied, follow-up data covering a period of 4 years are available.

In addition, 160 healthy subjects matched by age and sex have been randomly selected within the general population as controls.

Fig. 1. Pedigrees of the 7 FAP families described in this study. Squares and circles denote males and females, respectively. A line through the symbol represents deceased members. The numbers shown below the pedigree symbols refer to the 36 individuals/patients examined, and described in Table 1. GS = Gardner syndrome. Key to the symbols: CC = colorectal cancer. FAP = familial adenomatous polyposis. CHRPE = congenital hypertrophy of the retinal pigment epithelium. Others = skin and/or bone lesions.
Table 1. Age of the subjects with or without FAP and association with the presence or absence of CHRPE.

<table>
<thead>
<tr>
<th>Subjects with FAP</th>
<th>Subjects without FAP</th>
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<td></td>
<td>S/F</td>
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<tr>
<td>1/1</td>
<td>32</td>
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<td>6/1</td>
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S/F = subject number / family number (see Fig. 1). F = female. M = male.
CHRPE + = presence of retinal patches. CHRPE – = absence of retinal patches.
Subjects number 3, 2 and 5 were not studied for FAP owing to their young age.

Table 2. Prevalence of FAP in the subjects pertaining to the affected families and its relation with CHRPE.

<table>
<thead>
<tr>
<th>Subjects with CHRPE (%)</th>
<th>Subjects without CHRPE (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with FAP</td>
<td>7 (43.75)</td>
<td>5 (29.42)</td>
</tr>
<tr>
<td>Subjects without FAP</td>
<td>9 (56.25)</td>
<td>12 (70.58)</td>
</tr>
<tr>
<td>Total</td>
<td>16 (100)</td>
<td>17 (100)</td>
</tr>
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Subjects showing CHRPE areas (Table 2). It should be noted that only 43.75% of patients affected by CHRPE were affected by FAP as well. On the other hand we want to point out that 29.42% of the patients without CHRPE were affected by FAP.

The lesions found in 19 patients with CHRPE amount to 85 in total; 11 patients had lesions in both eyes (57.89%). None of the patients complained of ocular symptoms associated with lesions of the retinal pigment epithelium.

We have divided CHRPE areas into 3 categories according to their size as related to the diameter of the optical disc: A) 14 lesions (16.47%) the size of which are greater than or equal to one disc diameter: they are roundish, dark with internal clear areas (caused by the atrophy of the retinal pigment epithelium), through which the choroid vessels may be seen. The margins may be masked by clear halos; they are present either at the posterior retina or immediate retinal periphery. B) 4 lesions (4.70%) the size of which are approximately equivalent to half disc diameter: elliptic shape, variously pigmented and marked by clear fish-tail halo. These lesions were found in the medium retinal periphery. C) 67 lesions (78.82%) smaller than half the disc diameter: they are small pigmented spots, often surrounded by a clear halo, in the medium or extreme retinal periphery.

Angiographic features
One female patient was examined by means of retina fluorescein angiography; this was not done for diagnostic purpose, but it was aimed at a more thorough study of CHRPE.

Lesions showed hypofluorescent areas, due to the ‘mask effect’ resulting from hypertrophy of the retinal pigment epithelium, as well as hyperfluorescent areas due to the ‘window effect’ resulting from the rarefaction or atrophy of pigmented epithelium; the vascular net of the choroid was clearly visible inside the latter (Fig. 2). No alteration of the retinal capillary caliber over CHRPE areas described by Blair in his study was observed (Blair & Trempe 1980).

Differential diagnosis
The congenital lesions of the retinal pigment epithelium (CHRPE) found in members of a family affected by FAP are to be considered separate from the following retinal lesions: A) Congenital multifocal hypertrophy of pigmented epithelium (bear tracks): multiple areas, often bilateral with a typical layout. B) Congenital unilateral and solitary hypertrophy of pigmented epithelium, often characterized by anomalies of the retinal circulation (Cohen et al. 1993). C) Benign choroidal nevus. D) Malignant choroidal melanoma. E) Scars from chorioretinal infections, for example toxoplasmosis.

Fig. 2. Angiographic image of CHRPE (female aged 24 years).
Follow-up
As regards the 13 subjects (7 females and 6 males) included in the first 4 family groups studied, follow-up data available cover a period of 4 years. During this period no gastrointestinal and ophthalmological changes were observed in all patients; in particular, no numerical and/or qualitative modifications of CHRPE areas were observed.

Study on CHRPE prevalence in population
Some authors have included in their studies a group of patients for control purposes; these groups consist, as a maximum, of 40 subjects whose CHRPE prevalence percentage were very different, i.e. from 0% (Berk et al.) to 31.8% (Traboulsi et al.) (Berk et al. 1988; Chapman et al. 1989; Salvi et al. 1989; Traboulsi et al. 1987).

In a study on CHRPE prevalence within draftees, Murgia et al. ascertained a percentage of 1.4%; the study was extended to 450 male subjects sent for selection to the Medical Team of Milano Military District (Murgia et al. 1992).

We took, for control purpose, a group of 160 subjects of same age and sex, randomly chosen in the normal population. Of them, 151 subjects (94.5%) presented no CHRPE areas, whereas 9 subjects (5.5%) had CHRPE areas: 7 (4.3%) had monolateral lesions and 2 (1.2%) had a bilateral lesion. In all cases they were limited CHRPE areas, the definition of which was less than half disc diameter (category C), well pigmented and located in the medium-external retina periphery. None of the positive subjects presented a positive anamnesis for FAP.

Discussion
FAP is transmitted by an autosomal dominant gene located on the long arm of chromosome 5, known as APC gene (Adenomatous Polyposis Coli) (Bodmer et al. 1987).

Molecular genetic studies have confirmed the potential accuracy of the pre-symptomatic FAP diagnosis in subjects at risk; this diagnosis can be made using polymorphic DNA markers associated with fundus oculi examination in order to ascertain the presence of lesions affecting the retinal pigment epithelium (Mac Donald et al. 1992).

The lesions defined as congenital because they were observed examining a 3-month-old baby (Traboulsi et al. 1987) are seemingly due to the lack of synthesis of a protein regulating growth and cellular replication (Bodmer et al. 1987).

The term ‘congenital hypertrophy of retinal pigment epithelium’ (CHRPE) has come into use even though histopathologic findings have pointed out that the term ‘hamartomas of the retinal pigment epithelium’ would be more appropriate (Kasner et al. 1992).

In recent years several studies have been carried out to determine the relationship between FAP and CHRPE. According to them a very high correlation seems to exist between CHRPE and FAP. In some of the reported studies all FAP patients examined were also affected by alteration of pigment epithelium (Chapman et al. 1989; Diaz Llopis & Menezo 1987; Salvi et al. 1989).

Within the families that we studied, it was ascertainment that out of the 16 patients with CHRPE 43.75% were also affected by FAP. However, it should be noted that 2 patients are young (age 13 and 16 years) and might develop polyposis in future, therefore, the above percentage may increase. Moreover, we noticed that out of the 12 subjects affected by FAP, 58.33% presented CHRPE areas. These percentages are lower than those reported by other authors (Berk et al. 1988; Chapman et al. 1989; Diaz Llopis & Menezo 1987, 1988; Heyen et al. 1990; Romania et al. 1989; Salvi et al. 1989), but similar to Iwama et al’s results, who, however, distinguished between Gardner patients and FAP patients (Iwama et al. 1990). Our observations reduce remarkably the predictive value of CHRPE detection within a known family.

The presence or absence of the CHRPE phenotype in at risk persons might be due to the different positions of the APC gene mutations along the coding sequence, as reported by Olschwang who systematically found CHRPE presence if the mutations occurred after exon 9, and this may explain the considerable difference between the frequencies of CHRPE observed in various papers (Olschwang et al. 1993).

As far as the specificity of CHRPE findings is concerned it is interesting to note that a large molecular genetic population based study performed on 33 FAP families showed a high specificity of ophthalmological examinations in low-risk individuals, allowing for a reduction of colonoscopy screening in these subjects (Maher et al. 1993). In our study it should be considered that out of 160 healthy controls only 5.5% were found to have hypertrophy spots of retinal pigment epithelium and limited only to type ‘C’, as defined above. Consequently, if we find a subject with type ‘A’ or ‘B’ CHRPE in the general population, it might be quite probable that he/she is a carrier of a mutated APC gene. Such a finding, even though fortuitous, would require further thorough examination for diagnostic purpose.

Retinal examination shows high specificity (low false positive rates), but low sensitivity (high false negative rates). For these reasons, in conclusion, we suggest that without the availability of molecular genetic analysis, a combination of clinical procedures should be carried out for screening purposes in at-risk FAP individuals.

Acknowledgment
We thank Dr M. Clementi, Medical Genetics Service, University of Padova School of Medicine, for providing us with the computer program GENE, to draw the pedigrees in Fig. 1.

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Received on February 10th, 1995.

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