# ASSESSMENT OF THE VALUE OF CONGENITAL HYPERTROPHY OF THE RETINAL PIGMENT EPITHELIUM AS AN OCULAR MARKER FOR FAMILIAL ADENOMATOUS POLYPOSIS COLI

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## SUMMARY

**The presence of bilateral, multiple patches of congenital hypertrophy of the retinal pigment epithelium (CHRPE) is cited as an early phenotypic marker of the familial adenomatous polyposis coli (FAPC) gene. However, the degree of concordance between CHRPE and the presence of familial adenomatous polyposis (FAP) has not been adequately assessed in individual families. We studied the eyes of 28 members of a single kindred spanning three generations with FAPC; 14 were affected and 14 unaffected but 'at risk'. Six affected and 8 unaffected at risk individuals possessed a total of 34 retinal lesions, 17 in each group. Two affected individuals and 1 at risk individual had the classical pattern of CHRPE associated with FAPC. The sensitivity of CHRPE as an ocular marker for FAPC in this kindred was 14.2%. Our findings have implications for the use of CHRPE for the presymptomatic screening of family members at risk of FAPC. Therefore, ocular examination should not replace colonoscopic screening in an individual at risk of FAPC.**

Inherited gastrointestinal polyposis syndromes include Gardner's syndrome,[1] familial polyposis coli[2] and Turcot syndrome. The gene for familial adenomatous polyposis coli (FAPC) has been linked to chromosome 5q21,[3–6] and point mutations at this locus are responsible for familial adenomatous polyposis (FAP) and Gardner's syndrome.[6] The development of multiple adenomatous polyps in the gastrointestinal tract of affected individuals, with 100% malignant potential, characterises these conditions.[2,7] Extracolonic manifestations (e.g. osteomas, fibromata and sebaceous cysts) are features of Gardner's syndrome.

Multiple patches of congenital hypertrophy of the retinal pigment epithelium (CHRPE) have been described in large numbers of individuals with Gardner's syndrome[8–14] and FAP.[15–22] CHRPE was originally used by Reese and Jones[23] to describe congenital benign melanomas of the retinal pigment epithelium, but has become associated with the pigmented retinal lesions found in FAPC. The presence of bilateral, multiple patches of CHRPE is cited as an early phenotypic marker of the FAPC gene.[13]

Some authors consider CHRPE as a discrete ocular marker for FAPC in families in which it occurs.[9,13,19] On the basis of CHRPE's reported high sensitivity as an ocular marker for FAPC[10,20,24] its presence has been advocated to complement DNA linkage studies in a presymptomatic diagnosis of FAPC.[24–26]

Evidence exists for interfamilial variation in CHRPE[27] and intrafamilial variation has been suggested.[11,14,22,27] Therefore, could the absence of retinal lesions in an individual belonging to a kindred with some family members possessing CHRPE indicate the absence of the FAPC gene? To answer this important question three generations of an extensive kindred (Fig. 1) with FAPC were examined.

## SUBJECTS AND METHODS

Twenty-eight members of a single kindred spanning three generations with FAPC were studied. Diagnosis was made by symptomatic presentation or by the finding of multiple colonic polyps at colonoscopic screening. Fourteen affected and 14 'at risk' but unaffected first degree relatives were included in the study. There was an equal sex distribution in each group.

Each subject had a full medical and surgical history taken which included mode of presentation (symptomatic or at colonoscopic screening, i.e. asymptomatic: Table I), age at diagnosis, history of extracolonic features and treatment. A full ophthalmological examination included Snellen visual acuity, slit lamp biomicroscopy, and fundal examination after dilatation with the indirect ophthalmoscope and 90 dioptre lens. Informed consent was obtained from all patients, or the parents if the patient was a minor.

Retinal lesions were classified according to type:[18,22]

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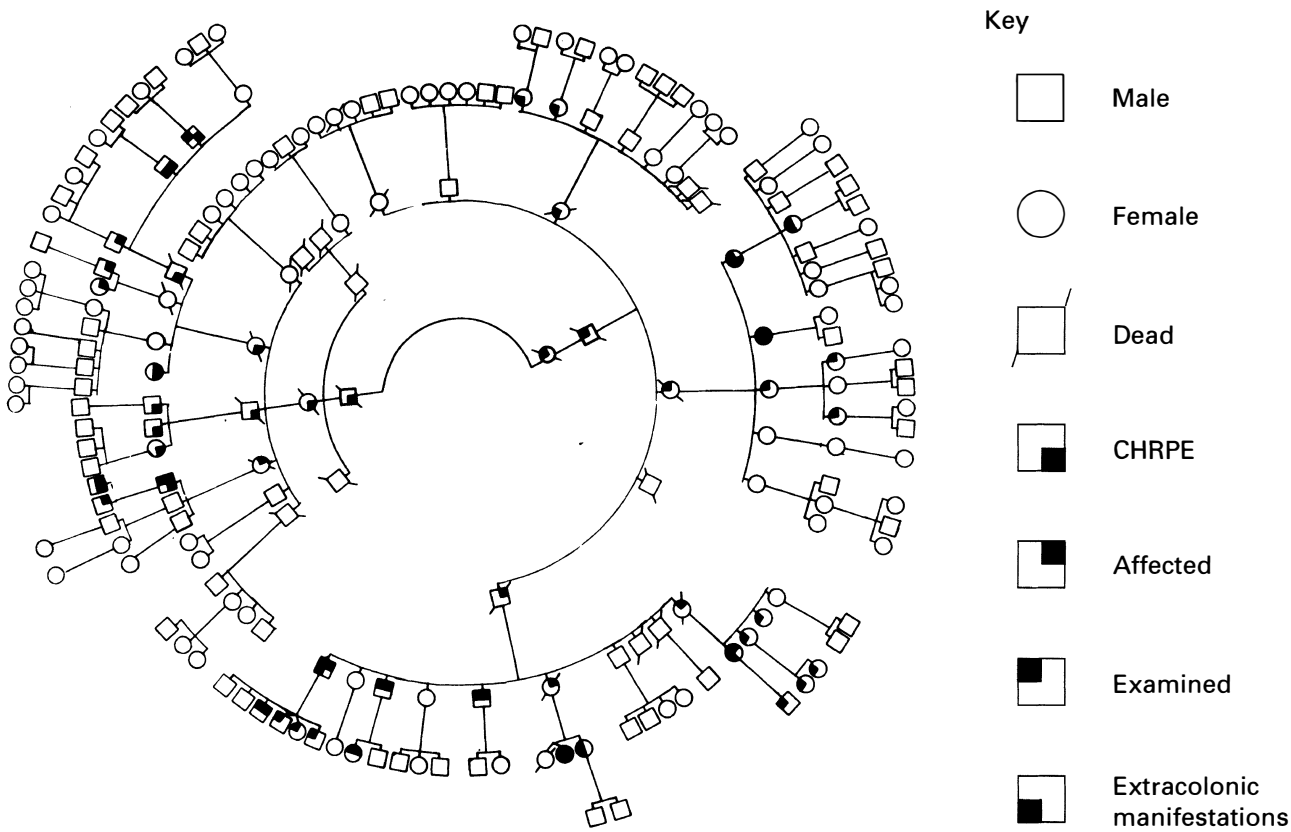


**Fig. 1.** *Pedigree of FAPC patients with and without extracolonic manifestations and retinal lesions.*

a. Oval pigmented lesion with surrounding pale halo.
b. Small round pigmented dot.
c. Large pigmented spot.
d. Large atrophic lesion with or without a pigmented halo.

The location (superior, inferior, nasal or temporal) of each lesion was recorded and the number of lesions in each eye. Typical and atypical lesions were photographed.

## RESULTS

Six of the 14 affected individuals possessed 17 retinal lesions consisting of mainly type b lesions (Table I). Only 2 affected individuals met the criterion of four or more lesions in one or both eyes to be considered positive for CHRPE.[14,21,26,27] Eight of the 14 at risk unaffected individuals possessed 17 retinal lesions of which 13 were type b (Table II). One individual met the criterion to be considered positive for CHRPE and also had two depigmented lesions.

**Table I.** Type and number of retinal lesions in each affected individual

| Case no. | Age (yr) | Presentation[a] | Right eye | Left eye | Extracolonic manifestations |
|---|---|---|---|---|---|
| 1 | 57 | A:44 | 2b, 1d | – | + |
| 2 | 53 | S:40 | 5b | – | + |
| 3 | 49 | S:22 | 1b | – | + |
| 4 | 49 | A:38 | – | – | – |
| 5 | 48 | S:34 | – | Choroidal naevus | – |
| 6 | 47 | S:34 | – | – | + |
| 7 | 47 | S:44 | – | – | – |
| 8 | 34 | S:26 | 2b | 3b | + |
| 9 | 30 | S:19 | – | – | + |
| 10 | 29 | A:24 | – | 1b | – |
| 11 | 27 | A:25 | – | – | – |
| 12 | 20 | A:20 | – | – | – |
| 13 | 20 | A:16 | 1b | 1 depigmented | – |
| 14 | 17 | A:14 | – | – | – |

[a]A, asymptomatic (detected at colonoscopic screening); S, symptomatic; a, b, c, d, type of retinal lesion.

**Table II.** Type and number of retinal lesions in each unaffected at risk individual

| Case no. | Age (yr) | Right eye | Left eye | Extracolonic manifestations |
|---|---|---|---|---|
| 1 | 36 | – | Choroidal naevus | – |
| 2 | 29 | – | – | + |
| 3 | 29 | 1b | 1b; less dense b | – |
| 4 | 26 | 2 depigmented | 3b; 1a | – |
| 5 | 26 | – | – | – |
| 6 | 21 | – | 1b | – |
| 7 | 19 | – | 1b | – |
| 8 | 19 | – | 2b | – |
| 9 | 19 | – | 1b | – |
| 10 | 17 | – | – | – |
| 11 | 14 | – | – | – |
| 12 | 13 | – | – | – |
| 13 | 9 | 1b | – | – |
| 14 | 7 | – | 2b | – |

a, b, type of retinal lesion.

## DISCUSSION

The study of this single pedigree, with an extensive family history of FAPC, clearly demonstrates marked intrafamilial variation of CHRPE in some families, as suggested by other workers.[11,14,25,27] A complete absence of CHRPE in subjects with FAPC has been recorded.[9,10,11,21,22,28] Despite

this, some authors consider CHRPE as a discrete ocular marker for FAPC[13,21] in families in which it occurs.

Examination of 28 members of this family demonstrated only 3 subjects (Fig. 1) who met the criterion to be designated positive for CHRPE. One of these individuals was unaffected but at risk of FAPC, and also possessed one type of lesion considered by some authors as even stronger evidence for the inheritance of the abnormal gene.[18,22]

This study demonstrated a diagnostic sensitivity of 14.2% for the presence of CHRPE, indicating that in certain families CHRPE is not a reliable ocular marker for the FAPC gene. Therefore, to answer the question posed in the introduction, an individual without CHRPE in a family with some affected members possessing CHRPE, cannot be excluded from colonoscopy on ocular examination. The findings of this study also have implications regarding the use of combined CHRPE and DNA linkage screening in the presymptomatic diagnosis of FAPC.

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