Can CHRPE Be Used To Diagnose New Cases of Familial Adenomatous Polyposis?

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Introduction:

Multiple patches of congenital hypertrophy of the retinal pigment epithelium (CHRPE) have been described in large numbers of individuals with Gardner syndrome and Familial adenomatous polyposis (FAP) [1-6]. Although CHRPE was first described by Reese and Jones in 1956 [7], its association with Gardner syndrome was only described by Blair and Trempe in 1980 [8]. The condition does not affect sight and has no malignant potential. Other extracolonic manifestations of Gardner syndrome include benign osteomas of the long bone and the skull (in particular jaw bones), dental abnormalities epidermoid skin cysts and desmoid tumours [9]. The value of CHRPE as a predictive congenital phenotypic marker in FAP kindreds is well recognised with a strong correlation between the genotype and the phenotype (fig 1). CHRPE is usually only present in FAP patients with mutations between codons 463 and 1387 in the *APC* gene [10-15] and is estimated to occur in 60% of FAP families [8] (fig 2).

The majority (81%) of CHRPE in FAP kindred are hyperpigmented lesions compared with 5% hypopigmented lesions. The remaining 14% of lesions are found to have a mixture of hypo and hyperpigmented lesions[16]. Generally the lesions are distributed in all four quadrants of the retina with the smaller lesions located peripherally and the larger lesions located posterior to the vortex veins. Lesions may be bilateral or as a solitary oval patch (fig 3).[1, 2, 5] There have been attempts to define clinically reliable methods for the assessment of FAP-related CHRPE. For example, Morton et al. described a diagnostic criteria in which lesions were considered significant if they were 1) bilateral, 2) three or more in number and 3) any greater than 0.3 optic discs in diameter (sensitivity of 84% in positive examinations). Another author proposed that only oval pigmented areas with a surrounding depigmented halo (“*type A”)* should be considered pathognomonic of FAP as it was found in two thirds of the FAP group and none in the control.[6]

CHRPE is a common incidental finding on ophthalmoscopy, present in 1-40% of the general population [17, 18]. Based on retinal examinations, CHRPE are generally classified into four types: oval, pigmented, and surrounded by a halo (type A); round, small, and pigmented (type B); round, large, and pigmented (type C); and round, large,

and depigmented (type D)[2]. Of these, pigmented dot lesions are the commonest type, accounting for 92.5% of all CHRPEs [18]. Grouped, but unilateral variants of CHRPEs are also recognised and include multiple pigmented plaques characterised by a larger lesion surrounded by several smaller ones, resembling the paw and toes of an animal ("bear tracks" or congenital grouped pigmentation of the retinal-pigmented epithelium) (fig 4). Bear track lesions are thought not to be related to FAP by several histological studies[19-21]. A significant proportion of FAP cases (~25-30%) result from new mutations (with no previous family history). Clearly, these could present as incidental CHRPE. At present, we have no reliable data on the contribution of such cases to the frequency of incidental CHRPE. However, of an early study 1-3 CHRPE can occur in the General Population without FAP as 2/94 controls had 3 CHRPE.[22]

Hypothesis: Congenital hypertrophy of the retinal epithelium (CHRPE) is considered to be a pre-adenomatous phenotypic marker for familial adenomatous polyposis (FAP) mutation carriers. Presence of CHRPE can be used clinically to detect asymptomatic carriers in FAP proven families prior to genetic testing. As approximately 25% of FAP cases result from new mutations, FAP may occasionally need to be excluded amongst incidental cases of CHRPE. However, CHRPE may be common in the general population and the great majority of apparently isolated CHRPE may not be due to constitutional APC mutation.

- CHRPE occurs with central mutations in APC
- 70-80% of all APC mutation carriers
- However risk of APC is not known in individuals with no FAP FH and no bowel symptoms referred from ophthalmology
- *De novo* mutation rate for APC about 1 in 80,000 births
- Only 1 in 100,000 will have CHRPE
- 1-3 CHRPE can occur in Gen Pop without APC -2/94 controls had 3
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- Bear track CHRPE not characteristic of APC
- Population frequency of CHRPE not known –if > 1 in 100 <0.1% of isolated CHRPE will have APC
- Need to assess what proportion of isolated CHRPE have *de novo* APC mutations
- **All cases of isolated CHRPE referred to each service**
- Number of lesions and type (bear track or not)

- APC testing and endoscopy

Method:

Individuals with CHRPE who are referred for assessment in order to exclude FAP are reviewed. Detailed interview of bowel symptoms, reconstruction of pedigree, confirmation of CHRPE, selective endoscopic colonic evaluation, and genetic testing were carried out in order to determine the possible diagnosis of FAP.

1. Age
2. Type of CHRPE (bear track or usual)
3. APC mutation testing
4. Endoscopy results

Local Identifier	Age assess-ment	No FH FAP	No bowel symptoms	No of Typical CHRPE (B)	No of Halo CHRPE (A)	No of Oval Large CHRPE (C)	No of Bear track	Laterality	APC testing	Endoscopy

- To qualify must have no FH FAP and no bowel symptoms

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