Genetic heterogeneity of congenital hypertrophy of the retinal pigment epithelium (CHRPE) in families with familial adenomatous polyposis

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Abstract

One hundred and eighteen subjects with familial adenomatous polyposis (FAP) and 80 of their relatives who were at low risk (<0.01) of carrying the FAP gene were scored by one of us (BJ) or by colleagues to assess the frequency of congenital hypertrophy of the retinal pigment epithelium (CHRPE). A CHRPE is defined as an "oval pigmented lesion surrounded by depigmented halo". Seventy five (63.6%) of the FAP cases and one (1.2%) of their relatives had at least one CHRPE. There was no systematic difference in the number of CHRPEs in the left and right eyes so all analyses are based on total number of CHRPEs and the findings were highly correlated ($p=0.001$ for a test of no correlation). There was also no evidence of any age effect in total number of CHRPEs in affected subjects. In 26 families there was more than one subject affected with FAP. There was a significant common family effect with respect to CHRPE expression for total number of CHRPEs with an F statistic of 1.73 ($p=0.02$ for a test of no family aggregation) indicating that family members are more similar to each other than to affected subjects from other families. This may indicate that specific mutations play a role in determining the number of CHRPEs. Nine affected subjects had intra-abdominal desmoids, and in these the frequency of each of the types of CHRPE was no higher (in fact, slightly lower) than the average for affected subjects without desmoids, but this difference was not significant ($p>0.3$).

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The occurrence of pigmented lesions of the retina in several affected members of one family with Gardner syndrome was first described by Blair and Trempe¹ in 1980. These retinal lesions have become known as CHRPE (congenital hypertrophy of the retinal pigment epithelium) and are characteristically ovoid or round discrete lesions, 0.1 to 1.0 or more disc diameters (150 μ m to 1.5 mm or more) in size, and frequently have a depigmented halo around them. Smaller round pigmented lesions, less than 150 μ m in diameter may be found in normal subjects, but rarely more than three in one person.^{2,3} Histologically the char-

acteristic retinal lesions appear to be choristomas⁴ or hamartomas,⁵ while the small black retinal lesions consist of enlarged pigment epithelial cells containing enlarged, spherical pigment granules, an appearance similar to that of isolated patches of congenital hypertrophy of the retinal pigment epithelium.⁵

Multiple CHRPEs are found in the retinae of a high proportion of patients with FAP, both in those with many extracolonic features of the disease (Gardner syndrome) and in those with few such extracolonic lesions.⁶ The proportion of cases of FAP who manifest significant numbers of CHRPE varies in different recent series from 66 to 92% (66%,⁶⁻⁸ 80%,⁹ 87.5%,¹⁰ 92%³). The presence of three lesions in the retinae of a subject at risk of inheriting the gene for FAP was estimated to give a 2/3 probability of carrier status, while more than three was diagnostic.³ The presence of bilateral multiple retinal lesions as a marker for FAP with extracolonic manifestations was calculated to have a specificity of 0.95 and a sensitivity of 0.78.¹¹

Retinal lesions in patients with FAP have been classified into five types, but it is the oval pigmented lesion with a pale halo that is unique to FAP.^{9,10} Small pigmented black dots in the periphery of the retina, the most common lesion in FAP, also occur in normal subjects, but in these normal subjects more than three lesions are rarely found.³

The difficulty with using the presence or absence of CHRPE as a diagnostic tool in those at risk of FAP stems from the possibility that in some families there is no expression of CHRPE in affected subjects. Various authors have addressed the question of whether there is genetic heterogeneity in FAP with some families expressing CHRPE and some not, or whether there is variability within the same kindred with regard to the expression of CHRPE. Most authors subscribe to the concept of heterogeneity, with about one-quarter of families showing non-expression of CHRPE in affected subjects (15%,⁷ one third,⁶ 35%¹²) while other families showed almost 100% expression of CHRPE. A number of authors have found a higher proportion of CHRPE in patients with FAP and with extracolonic features than in those without.^{10,13} Since this question is of great importance when the presence of CHRPE is used as a clinical tool for predictive testing, we set out to determine whether there was genetic heterogeneity with respect to CHRPE in the FAP families ascertained by the Polyposis Registry in London. We have also noted those subjects in whom

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desmoids have occurred and correlated this with the CHRPE findings.

The recent identification of the gene for FAP should soon allow the detection of the specific mutations in the gene in different families and it may then become possible to correlate the presence of a specific mutation with the clinical expression of CHRPE and other extracolonic manifestations of FAP in particular families.

Table 1 CHRPE lesions in affected subjects from families in which more than one affected person was typed

Family	DoB	CHRPE	
		R	L
4	1926	010X0	01080
	1924	01000	02000
	1955	01000	01000
	1954	21000	02000
	1953	00000	00000
10	1955	23000	11000
	1968	03000	01010
	1943	34000	1X000
	1930	11010	02010
	1968	13000	05000
19	1948	20000	31000
	1923	08003	12212
	1971	01410	10210
	1967	05010	31000
	1937	00000	00000
33	1966	00000	00000
	1968	01100	00000
41	1934	05100	16001
	1975	00000	00000
54	1953	03020	02000
	1912	05000	04010
63	1946	12000	01010
	1945	00000	00000
	1969	04000	00000
	1952	00010	02000
	1938	13000	21010
75	1971	22000	22000
	1934	18001	2X000
79	1964	02000	11000
	1951	00000	00000
82	1943	01010	11000
	1975	30000	20000
84	1957	10000	11000
	1940	11100	00102
86	1967	3200?	2100?
	1935	12000	03000
100	1969	20000	01000
	1971	03000	05100
117	1951	21000	34000
	1947	1X000	15100
152	1938	01000	01000
	1962	11000	00000
230	1960	00000	01001
	1954	1X001	08100
236	1969	32010	55010
	1935	13000	04100
244	1966	12000	10000
	1948	04000	13000
271	1924	13100	13000
	1960	02000	01000
286	1924	12000	15000
	1963	01000	03000
253	1947	00020	20000
	1948	06000	0X000
362	1957	02100	01001
	1940	11000	11000
391	1971	0X001	34000
	1969	30033	02011
398	1966	04100	4X200
	1963	31200	23100
468	1971	00000	02000
	1973	10000	00000
501	1939	0X000	1X000
	1963	22030	01020
	1960	02000	13000
	1934	26000	38000
	1954	00000	00010
	1961	02000	01010
	1974	00000	00100
	1970	04000	00000
	1972	00000	01000

The lesions in each eye were tabulated using a five digit code, each digit indicating the number of each of the above groups of lesions (for example, 15000 would indicate an eye with one type (a) lesion, five type (b) lesions, and no types (c), (d), or (e) lesions).

X denotes more than ten lesions of that type.
DoB = date of birth of affected subject.

Patients and methods

FAP cases were ascertained from the Polyposis Registry at St Mark's Hospital. The diagnosis in all cases was confirmed by pathological examination of the colon, with the finding of more than 100 adenomatous polyps in the colon being taken as diagnostic of the condition. Nine of the affected subjects were diagnosed clinically as having intra-abdominal desmoid disease. Screening for desmoids by abdominal ultrasound was not routinely performed. In 26 families we were able to examine more than one affected subject from the same family.

At risk relatives were examined by sigmoidoscopy from their early teenage years, and linkage analysis (or mutation delineation) performed on DNA from blood samples, by standard techniques. The results were analysed taking into account the relationship to the patient of the person at risk, and the person's age, to obtain an estimate of the risk to that relative of having inherited the FAP gene.³

One hundred and twenty affected subjects and 81 at risk relatives (at less than 1% risk on linkage and clinical grounds of having inherited FAP) were examined either by one of three ophthalmologists who made the original report of this series⁹ or by one of the present authors (BJ) by binocular indirect ophthalmoscopy. The retinal lesions were classified into five types, a modification of that described by Berk *et al.*¹⁰

The five groups are: (a) oval pigmented lesion surrounded by depigmented halo; (b) small round pigmented spot; (c) large pigmented area in pigment epithelium; (d) small depigmented window lesion; (e) large atrophic lesion of pigment epithelium and choroid.

STATISTICAL METHODS

All comparisons concerning the distribution of the number of CHRPEs were made using the appropriate χ^2 test. The differences between the distribution in the left and right eyes was assessed using a paired *t* test. Similarity between affected sibs was assessed using ANOVA.¹⁴

Results

Of the 120 patients with FAP who were examined, one had retinitis pigmentosa, and one had toxoplasmosis in the fundi, but the rest (118 subjects) were scored with respect to CHRPE. Table 1 shows the CHRPE results for affected subjects from families in which more than one affected person was typed. Seventy five affected subjects (63.6%) had one or more large oval pigmented lesion (type (a) lesion) and a further 32 had at least one lesion of type (b), (c), (d), or (e), but no type (a) lesion. In total, then, 107 affected subjects (90.6%) had one or more lesions of any kind. Eighty one at risk relatives were examined, all of whom were at low risk of FAP (<1%). Of these, one had one type (a) lesion (1.25%), 22 additional subjects had one or more other

CHRPE lesions (21.2%), and 57 had no CHRPE lesions (70.4%).

There was no systematic difference between the left and right eyes of cases ($p > 0.14$ for all comparisons) so the total number of lesions was computed for each subject by lesion type. Table 2 summarises the distribution of the number of CHRPEs identified by subject status. For each subject the total number of lesions in both eyes is combined. Investigation using linear regression of total number of CHRPEs with age showed no relationship for any of the five types of lesions ($p > 0.12$ for all comparisons).

Comparisons between the affected FAP patients and their low risk relatives showed highly significant differences, with patients having more CHRPEs on average for each classification ($p < 0.001$ for each comparison).

There was evidence of a within family correlation ($p = 0.02$) for the number of type (a) lesions in affected family members. The F statistic from the ANOVA table was 1.73 which implies an intraclass correlation of 0.27. Thus family members are significantly more similar in terms of CHRPE count than non-family members, but the similarity is not extensive. Table 3 summarises the frequency of family members with type (a) lesions among the families by the number of affected relatives.

Table 2 The distribution of the number of CHRPEs among FAP patients. For a description of CHRPE type see text

Type of lesions	No of lesions (%)				
	0	1	2	3-4	5+
(a) Affected	43 (36)	26 (22)	18 (15)	21 (18)	10 (9)
Low	80 (99)	1 (1)			
(b) Affected	22 (18)	15 (13)	14 (12)	26 (22)	41 (35)
Low	63 (76)	14 (17)	4 (5)	2 (2)	
(c) Affected	94 (80)	13 (11)	6 (5)	3 (2)	2 (2)
Low	76 (95)	1 (1)	1 (1)	2 (3)	
(d) Affected	94 (80)	15 (12)	5 (4)	2 (2)	2 (2)
Low	77 (95)	2 (2)	2 (2)		
(e) Affected	104 (89)	8 (7)	3 (3)	1 (1)	1 (1)
Low	79 (99)	1 (1)			

Affected = affected FAP patients.
Low = relatives of FAP patients at low risk (<1%) of FAP estimated by pedigree analysis and linkage.

Table 3 Distribution of type (a) CHRPE subdivided by the number of affected subjects per family

No of affected in family	No with type (a) CHRPE in family							
	0	1	2	3	4	5	6	7
2	2	6	7					
3	1	1	1	3				
4	0	1	0	1	0			
5								
6	0	0	1	0	0	1		

Table 4 The distribution of CHRPEs by presence or absence of desmoid disease in affected FAP cases. The p value shows the evidence for a difference in the distribution of the number of CHRPEs by desmoid status

Lesion type	Desmoid disease						p value
	YES			NO			
	No of CHRPE						
	0	1-2	3 or more	0	1-2	3 or more	
a)	3	3	3	40	41	38	1.00
b)	1	2	6	21	27	61	0.78
c)	8	1	0	86	18	5	0.67
d)	6	3	0	88	17	4	0.35
e)	9	0	0	96	10	2	0.57

Of particular note are the three families with three affected members who are CHRPE positive, as well as the family with six CHRPE positive family members out of six affected. The other classifications of CHRPEs showed no evidence of family aggregation.

A comparison of the nine FAP patients with desmoids and the 109 without desmoids showed no evidence of a difference for each of the five classifications of CHRPEs (table 4). Indeed for each of the five classifications, patients with desmoids had fewer CHRPEs than patients without desmoids, but the differences were not significant ($p > 0.3$ for each comparison).

Discussion

The findings in this study confirm the relative specificity of type (a) lesions (defined as large pigmented lesions with a surrounding halo) to FAP; one or more of these lesions occurred in 64% of gene carriers but in only 1.25% of their low risk relatives. The other CHRPE lesions were seen in an additional 27% of affected subjects (so that 91% of those affected had a CHRPE of some kind); however, 21% of low risk relatives also had minor (non-(a) type) CHRPE indicating that these lesions are much less specific for FAP.

This information has diagnostic use since identification of CHRPEs of any kind within at risk subjects modifies their risk of being a gene carrier. For instance, consider an at risk relative who has a prior risk of 50% of being a gene carrier. If that person is found to have one or more type (a) lesions, then, because type (a) CHRPEs are so common in carriers and so rare in non-gene carriers, the probability that this person is a gene carrier increases to 98%. Alternatively, if the person has none of the types of CHRPEs examined in this study, then the risk of being a gene carrier is reduced to 19% since only rarely do gene carriers not have any kind of CHRPEs. Only if lesions types (b) to (e) are identified in the absence of type (a) lesions is there limited diagnostic use since approximately an equal number of gene carriers and non-gene carriers fit into this category. Identification of only such lesions then implies that the carrier risk is essentially unchanged from the prior risk. However, concentrating on the type (a) lesions is sufficient to increase the risk to 98% for CHRPE positive subjects and reduce the risk to 27% for CHRPE negative subjects so that inclusion of type (a) CHRPEs is sufficient for most purposes. A further advantage of the type (a) CHRPEs is that for the age groups examined (in this series from 10 years of age), there is no evidence of any variation with age in the number of CHRPEs identified; thus examination for CHRPE in at risk subjects can be taken to be equally reliable.

The estimates obtained in this study could be combined with information from the results of endoscopy and molecular studies in a Bayesian calculation³ to provide a final age related risk estimate. We should note, however, in passing, that the usual assumption of the

Bayesian calculation is that the various signs under consideration occur independently of each other in gene carriers (and also in non-gene carriers) and that before we attempt to include further factors in the Bayesian calculation, their independence should be examined.

We showed a significant within family correlation for the presence of type (a) CHRPEs but the effect was not overwhelming. This suggests that different mutations in the gene causing FAP have differing probabilities of producing CHRPEs but that other factors must also play a role; to date, we do not have any information as to whether these factors are genetic. A natural question to ask concerns the use of this within family correlation for diagnostic purposes to refine further the calculations discussed above. The response is that while there is statistical evidence for the correlation, the effect within individual families is minimal and hence there is no value in including this information. For instance, if we concentrate on those 15 families with only two affected (table 3), we observed two families where neither affected person has type (a) CHRPEs, six where one had CHRPEs, and seven where both had CHRPEs. If there were no within family correlation then the expected numbers of such families would be 1.9 with no CHRPE positive subjects, 6.9 with one CHRPE positive member, and 6.1 with two CHRPE positive members, which is of course only minimally different from that observed. The majority of the information concerning within family aggregation for presence of CHRPE comes from four families in which all affected family members have CHRPEs; three of these families have three members while the other has six affected. This observation of a family with six CHRPE positive family members should only occur in 7% of families if there were no family aggregation. We might speculate then that at least some of these families have mutations which are more liable to produce CHRPEs; further studies must await the identification of the specific mutations in these and other families.

There have been conflicting reports in the past, some indicating that CHRPEs occur more commonly in subjects with FAP who

also have desmoid disease or other extracolonic manifestations than in those without,¹³ but others maintaining the opposite.⁷ In this series, nine affected subjects had serious desmoid disease; CHRPEs did not occur in all of these cases and overall were less common than among FAP subjects without desmoid disease (table 4). We could therefore find no relationship between desmoid disease and presence of CHRPEs.

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