Original articles

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

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Abstract

A polyposis register has been established in the Northern Region of England. A total of 48 families with 71 living affected subjects has been identified during the first three years of operation, a prevalence of 2.29×10^{-5} . Indirect ophthalmoscopy identifies the majority of gene carriers by showing multiple areas of congenital hypertrophy of the retinal pigment epithelium (CHRPE). The absence of this sign in families limits its value where a relative with CHRPE has not been identified. Combining eye examination with data on age of onset and linked DNA markers is highly effective in carrier exclusion; 38% of 528 first, second, and third degree relatives had their carrier risk reduced to less than 1 in 1000. Even with such assurance many subjects will request continued bowel screening at a reduced

frequency. Little interest has been shown in pre-natal diagnosis. The principal value of a genetic register with domiciliary nurse visiting is the reduction in early mortality among unrecognised gene carriers.

Familial adenomatous polyposis coli (FAPC) is a common autosomal dominant disorder characterised by multiple adenomatous polyps which develop, in particular, in the large bowel and show a marked propensity to malignant transformation. Following the recognition of its hereditary nature and the value of elective resection of the colon, diagnostic surgical registers began to develop. The first among these was the register at St Mark's Hospital, London where for over 50 years relatives at risk have been screened for the development of polyps by annual sigmoidoscopy.¹ The potential for manifestation of the disorder up to middle age has led to the adoption of a policy of bowel examination up to the age of 50 years. When polyps develop, elective resection of the colon with ileorectal anastomosis and surveillance of the rectum² is preferred generally to panproctocolectomy, which has the disadvantage of sphincter loss, and the ileal pouch,³ which is associated with a greater degree of surgical morbidity.

Adenomata in the upper gastrointestinal tract may undergo malignant change, particularly at the ampulla of Vater.⁴ Desmoid tumours of the abdomen constitute a rare but major complication,⁵ as do the occasional development of malignancies at other sites, including thyroid papillary adenocarcinomata, central nervous system tumours, and hepatoblastomata.^{6–8} Benign osteomata together with sebaceous cysts and intestinal polyps form the triad known as Gardner's syndrome.⁹ Recent molecular genetic evidence offers support to the clinical belief that Gardner's syndrome and FAPC are phenotypic variants of the same genetic

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defect.¹⁰ Cases of FAPC with brain tumours should not, however, be confused with the phenotypically distinct, and probably autosomal recessive, Turcot's syndrome.¹¹

The gene for FAPC was localised to 5q21 in 1987¹² and a variety of increasingly close polymorphic DNA markers have since become available.^{10 13 14} This has raised the possibility of exclusion of carrier status in family members without the need for annual bowel examination until middle age. For this to be effective, however, complete ascertainment and an understanding of probability calculation have become essential.

A clinical development of major relevance to the calculation of carrier risk has been the recognition of multiple areas of congenital hypertrophy of the retinal pigment epithelium (CHRPE) in heterozygotes. First identified in Gardner's syndrome,¹⁵ several studies have described it in FAPC regardless of other extracolonic features.¹⁶⁻²¹ The present study shows the clinical relevance of this sign and molecular genetic advances in a defined geographical population as a guide to the formation of effective genetic registers, which may bring about a significant reduction in the morbidity and mortality associated with this important disorder.

Materials and methods

The Northern Regional Health Authority serves a population of 3.1 million people with relatively little migration. There are two urban concentrations around Tyneside and Teeside comprising approximately two-thirds of the population. A registry of polyposis families was established in 1987 by the Northern Region Genetics Advisory Service in collaboration with the surgeons in the region. Under the direction of a consultant surgeon (AG) and the consultant clinical geneticist (JB), a genetic nurse (PC) was appointed to identify and visit all families known to have, or have had, a member with FAPC. With the active assistance of the region's 72 surgeons, the records of the surgical units were reviewed to identify FAPC patients known to them, and relatives who were being regularly screened. Seminars and lectures were instituted in the district hospitals to improve ascertainment.

In order to establish the value of ophthalmological examination, 66 affected subjects have been examined by indirect ophthalmoscopy after pupil dilatation by one of two ophthalmologists (CW and WC). Ninety-four adult controls were also examined. Indirect funduscopy produces a wider field of view than direct, though it requires a greater level of operator skill. In order to assess interobserver error, the first 20 in each group were examined separately by the two ophthalmologists. Despite mydriasis lasting up to four hours the investigation was well tolerated. The need to hold

a direction of gaze for several seconds limits use in young children.

Blood samples were obtained from available family members for analysis of linked polymorphic DNA markers. Principal use of the probes Pi227 and C11P11 was made during the first two years of study. Subsequently, the markers YN5.48 and ECB27 were added to the analysis.

The probability that family members carried the gene for FAPC was estimated in each case using traditional Bayesian calculation taking as conditional probabilities the age at which rigid sigmoidoscopy had proved normal, the results of eye examination, and, where informative, the results of DNA analysis.

In order to assess the likely impact of screening and perceptions of the disease together with attitudes to prenatal diagnosis and reassurance based on probability calculations, a group of gene carriers and their first degree relatives completed an attitude questionnaire.

Results and analysis

FAMILY ASCERTAINMENT AND EPIDEMIOLOGY

From a start of only 11 families known to the Regional Genetics Service or the registry at St Mark's Hospital, the initial review of surgical records yielded 18 new families. In total, only 21 relatives were having appropriate screening at the beginning of 1987. Ascertainment levelled and then rose steadily as the service became better known to surgeons and the benefits of family tracing became apparent. At the end of three years, 48 apparently independent families had been identified, containing 528 first, second, and third degree relatives. By the third year, 308 relatives had been reviewed and discharged or were undergoing continued surveillance.

In July 1990 a total of 71 living affected subjects was identified in the region. This represents a point prevalence of 2.29×10^{-5} or 1 in 43 662. If the 14 at risk relatives with six or more CHRPEs (see below) are included as definite gene carriers the point prevalence becomes 1 in 36 471. A retrospective analysis of the pedigrees showed that, in 1970, 1 in 24 000 living subjects was affected or would subsequently develop the disease.

CONGENITAL HYPERTROPHY OF THE RETINAL PIGMENT EPITHELIUM (CHRPE)

Fig 1 shows the results of examination of 66 obligate carriers, 151 at risk subjects, 10 of whom subsequently developed polyps, and 94 unaffected adult controls. The counts of CHRPEs included all hypo- and hyperpigmented lesions in both eyes regardless of size. None of the controls had more than three and none had lesions greater than 1 to 2 mm in diameter. In contrast, the affected subjects had up to 80 lesions. Fig 2 is a composite of the first 40 obligate carriers. The preponderance of small lesions at the periphery of the retina is apparent. In our series 92/94 controls

Figure 1 (Top) Histogram to show the total number of CHRPEs in controls, at risk relatives, and obligate gene carriers. (Bottom) An area of congenital hypertrophy of the retinal pigment epithelium. The size of the lesion and associated hypopigmented area in an at risk relative is virtually diagnostic of FAPC.

had none, one, or two small lesions and 2/94 had three lesions; 5/66 carriers (7.6%) had none, one, or two lesions, 3/66 (4.5%) had three lesions, and the remaining 58 (87.8%) had four or more lesions. Based on counts only, therefore, in our series a finding of fewer than three lesions represented a 1 in 13 probability of carrier status, three lesions gave a 2/3 probability of carrier status, and more than three was diagnostic. As a conservative figure for the purpose of risk calculation, it was assumed that a count of less than four small lesions represented a conditional probability of 1 in 10 of being a gene carrier.

The overall distribution of eye signs (fig 3) in the 141 polyp free relatives at risk reinforces the belief that most adults considered at risk are not, in fact, carriers of the gene.

Table 1 shows the distribution of gene carriers according to the presence or absence of typical

Table 1 Analysis of sensitivity of ophthalmological screening based on total number of CHRPEs in column 1, taking account of 'typical' hypo/hyperpigmented or large lesions in column 2, and making allowance for the presence of eye signs in relatives in column 3. The only 'missed' case in column 3 had no CHRPEs but her mother who had no polyps at 53 was found to have 17 CHRPEs and was, therefore, taken to be a non-manifesting gene carrier.

	All cases	All cases	Families with CHRPE+live member
0-3 CHRPEs	8	7	1
4 CHRPEs	1	0	0
5 CHRPEs	3	0	0
6+CHRPEs	54 (81.8%)	59 (89.4%)	58 (98.3%)
+/- pathological lesions			
Total	66	66	59

pathology and a CHRPE positive relative (see discussion). Two of the obligate gene carriers with a negative eye examination in our series were from the same family. The proband was identified at the age of 75 and his son was subsequently examined at the age of 48 and was found to have polyps. The four carriers who developed malignancy under 21 years of age had more than 10 CHRPE lesions and one of these was the only case with more than 80 lesions.

AGE AT DIAGNOSIS AND AGE AT ONSET

Colonic polyps were present at the first examination in all but 15 gene carriers and in consequence a precise age of onset could not be established. For the purpose of risk calculation, the age related risks shown in table 2 based on published data were used.

Table 2 A guide to the conditional probability of being a gene carrier given a negative bowel examination at each age (based on the published data of Murday and Slack²²). The original data extended only to 35 years and it was suggested that onset was unlikely beyond this age. We have, however, had one case with documented onset at 39 years and there are reports of rare cases with later onset or non-penetrance (see table 1). The original curve was extrapolated, therefore, following the same curve as that described by the original data. A multicentre analysis is under way which will provide a more precise and accurate age of onset curve.

Age in years	Probability	Age in years	Probability
12	5/7	26	1/11
13	5/9	27	1/12
14	1/2	28	1/14
15	2/5	29	1/16
16	1/3	30	1/19
17	2/7	32	1/24
18	1/4	34	1/28
19	1/5	36	1/38
20	2/11	38	1/50
21	1/6	40	1/66
22	1/7	42	1/100
23	1/8	44	1/150
24	1/9	46	1/200
25	1/10	48	1/500
		50	1/1000

Figure 2 Composite of 40 retinal charts to show the tendency for peripheral lesions to be smaller and hence more easily overlooked. A circle with a radius of half that shown contains only a quarter of all CHRPEs. Among obligate carriers as a whole, 470/720 (65.3%) were 'dot' lesions.

Figure 3 An analysis of 528 known first, second, and third degree relatives of FAPC probands. The combination of age at examination, eye examination, and DNA studies in subjects and their relatives reduced the probability of being a gene carrier in the majority with 38% falling below a risk of 1 in 1000 and 27% falling below a risk of 1 in 5000. The 6% with a risk approaching or equal to 100% probability had positive eye signs or unfavourable DNA markers but were bowel negative at the time of analysis.

Half of the gene carriers will have polyps on sigmoidoscopy at 14 years and 90% are positive by 25 years. Thus, a negative bowel examination at 25 years gives a subject a 1 in 10 conditional probability of being a carrier.

MOLECULAR GENETIC STUDIES

DNA analysis was performed on 175 members of the

21 pedigrees with suitable structure. A total of 1250 individual results were analysed for the *TaqI* polymorphism detected by the probe C11P11 (*D5S71*), the *BstXI*, *BclI*, *PstI*, and *MboI* polymorphisms detected by Pi227 (*D5S37*), the *BglII* polymorphism detected by ECB27 (*D5S98*), and the *MspI* polymorphism detected by YN5.48 (*D5S81*). At the time of calculation, YN5.48 was known to be flanking the gene in relation to the other probes. For the purpose of calculation a conservative estimate of recombination rates was used; a 5% crossover rate was assumed for YN5.48 with a 10% crossover rate for the other probes and a 0.5% probability of double crossover where flanking probes were informative.

Thirty-five of the 175 subjects tested were informative for probes on one side of the gene. The risk calculation was indirectly influenced in a further 35 of their immediate relatives as a result. Flanking markers were informative in only seven subjects*.

COMBINED RISK ESTIMATES

For the purposes of risk calculation, information from bowel examination, eye examination, and DNA analysis may be combined using traditional Bayesian calculation.^{23 24} The latter reference makes clear the benefit of combining information from different

*Dunlop *et al* (Lancet, 1991;337:313-6), using an additional two polymorphic markers and computer analysis, found 68% of 41 subjects to have informative flanking markers though this analysis was based on seven families selected for linkage study.

sources, a concept well established in genetics but not familiar to many other clinicians. Appendix 1 contains details of this technique.

Fig 3 shows the effect of combined probability calculation on the 528 family members with a 1 in 2, 1 in 4, or 1 in 8 risk on simple pedigree analysis; 38% had their risk reduced to less than 1 in 1000. Two-thirds of these had a residual risk of less than 1 in 20 000, which is of the same order of magnitude as that of the general population. A large proportion of this group were second or third degree relatives where the intervening relative had been shown to be healthy in middle age. They had not been formally approached to be offered screening and, clearly, such an approach would be inappropriate. Those still undergoing annual sigmoidoscopy may opt for its discontinuation or reduction to a lower frequency. The proportion in this category will inevitably rise rapidly as more informative and more closely linked markers become available.

FAMILY ATTITUDES

Attitudes to screening and prenatal diagnosis were assessed in 25 affected subjects, 27 spouses or unaffected parents, and 14 at risk subjects by face to face interview or, where this was not possible, by postal questionnaire. Each subject was asked to assess the level of risk at which they would feel it appropriate to discontinue screening. A range of risks was offered up to 1 in 5000 with a final alternative of 'never'; 21 of 25 affected, 21 of 27 parents/spouses, and 10 of the 14 at risk expressed the opinion that screening should 'never' be discontinued though most would accept checks every five years. This reaction reflects the deep seated fear of malignancy in these families. It is likely, however, that these proportions would be altered if subjects were advised in a more positive manner such as "I am more than 99.9% sure that you do not carry the gene". Nevertheless, it is clear that as long as markers are associated with even a small risk of error there will be considerable resistance to discontinuation of bowel screening. If a perfect prenatal diagnostic test were available, 15/25 (60%) affected subjects, 19/27 (70%) parents/spouses, and 11/14 (79%) at risk subjects would avail themselves of this. When asked directly, however, if they would consider termination of an affected fetus only four, six, and two respectively (12/66 or 18%) gave an affirmative response. It would seem likely, therefore, that there will be relatively few requests for prenatal diagnosis with a view to termination.

With one exception, respondents favoured commencement of bowel screening before the age of 16 years with approximately equal division between those who favoured the early teens and those who wanted their children screened as early as possible.

Discussion

EPIDEMIOLOGY

Attempts to determine the true incidence of FAPC²³⁻³⁰ have, in general, relied on the approximation that the proportion of deaths attributable to FAPC should reflect the number of births with this disorder. Probably the most reliable data are from the Danish register.³¹ Their life time risk was 0.97×10^{-4} . Their point prevalence rate was 2.60×10^{-5} , or 1 in 38 461, in 1982, based on 133 living FAP patients. Thus, in terms of point prevalence the present study compares favourably with the Danish study.

A practical guide in terms of register planning and audit would be that the incidence of FAPC is likely to be 1 in 10 000 and the point prevalence rate for manifesting carriers should be at least 1 in 30 000.

EYE EXAMINATION

Our experience with indirect ophthalmoscopy as a means of carrier detection was very favourable, with only 7.6% of obligate carriers having fewer than three lesions, while none of the controls exceeded this number. In other series occasional controls had four lesions and very rarely five lesions. In practice, therefore, first degree relatives were regarded as definite gene carriers if they had six or more, or if they displayed the typical large lesions, ranging up to one disc diameter, and with hypopigmented and hyperpigmented areas. If a first degree relative had fewer than four 'dots' on examination by one of our two experienced ophthalmologists, a conservative conditional probability of 1 in 10 was assigned. In centres without a large local series, a negative investigation must be regarded with more caution. In our series of obligate carriers, examination of 20 cases was performed by two independent ophthalmologists and the resulting fundal diagrams were almost identical. The ophthalmologists were not given clinical details before examination. Indirect funduscopy does require considerable skill, however, and it is essential that ophthalmologists are aware of the need to record every lesion. In our series, the ratio of tiny lesions described as 'dots' to larger lesions was 2 to 1. The ratio of lesions inside a circle with a half radius compared to the number outside that line in the retinal periphery was 1:3, that is, most lesions are at the edges and most are small. These ratios may be used to compare with retinal charts provided by other ophthalmologists. Ideally, all eye examinations should be performed by a single ophthalmologist in each region who should have an opportunity to examine a series of obligate carriers before starting formal screening of a high risk population for counselling purposes.

Traboulsi *et al*¹⁹ found multiple CHRPEs in 86.4% of gene carriers in 23 pedigrees, whereas five subjects from the three remaining pedigrees were negative for

this sign. Romania *et al*²⁰ found diagnostic numbers of retinal lesions in all 61 affected members of 34 pedigrees, with a range of four to 64. In the other 18 kindreds, which had a later mean age of onset, 32 patients were examined and none had more than three eye lesions. Polkinghorne *et al*²¹ found only 2/72 definite APC carriers to have no retinal lesions, but a relatively small proportion (62.5%) had six or more lesions. When morphology was added, however, at least 80% of their series could be assigned to the carrier group. They did not report an analysis of familial aggregation of the eye signs.

Thus, in a minority of FAP families, whose proportion of the total shows geographical variation, CHRPE lesions are consistently absent and in such families eye examination does not contribute to risk calculation. There is a suggestion that the presence of CHRPEs and possibly their total number is a reflection of a more aggressive form of the disease and there is a milder CHRPE negative form which may merge into the non-polyposis dominant colorectal cancer category. This is likely to be allelic in some cases in view of the recent observation of 5q allele loss in sporadic colon cancers.³²

OTHER EXTRACOLONIC FEATURES

There was no evidence in the present analysis to support a clinical distinction between FAPC and Gardner's syndrome. The use of orthopantomograms to detect jaw cysts has been put forward as a screening investigation,³³ though it presents problems with considerable interobserver error³⁴ and, in consequence, has not been used routinely in our register.

AUDIT

FAPC lends itself to audit by comparison of the number of families and persons known to each region. Ultimately, the success of regional registers may be measured on the basis of life expectancy. The dramatic increase in the number of relatives under surveillance in the Northern Region should have an impact, since retrospective analysis showed that of patients detected by screening only 1/25 (4%) had malignancy whereas among those detected on the basis of symptoms, 10/31 (32.3%) had a colorectal malignancy.³⁵ There is some prospective evidence of benefit; seven severely affected subjects, one of whom had carcinoma *in situ*, would not have undergone surgery had it not been for the genetic nurse. One case history illustrates the importance of a domiciliary family visitor. A 21 year old man had refused bowel examination despite being at 50% risk. His denial reaction was only overcome by some 40 hours of domiciliary contact. During this process he agreed to eye examination which showed multiple CHRPEs.

Figure 4 A 21 year old who had refused bowel examination despite having an affected parent but who agreed to colonoscopy after intensive counselling and a positive eye examination. He is shown three days after a colectomy with ileorectal anastomosis.

The impact of this was sufficient to overcome his resistance to endoscopy. Colonoscopy showed extensive polyposis which led to immediate colectomy. He is shown (fig 4) three days after surgery. He is now leading an active life with normal bowel action and has offered to meet others in need of psychological support.

More than half of gene carriers have polyps before 16 years and these may be symptomatic though there have only been six reports of malignancy.^{36 37} Nevertheless, these few reports, together with parental preference, make it clear that screening cannot be delayed into adulthood. The present practice is for children to be screened by the general surgeons responsible for the care of the family. Where a paediatrician skilled in the use of the paediatric colonoscope is available, a strong case can be made for children to be seen initially in this setting where there are more appropriate facilities for the management of young people. Though difficult to quantify, our clinical impression is that several young adults who reject screening have had adverse experiences when first referred. Males in early adolescence seem particularly sensitive to the stress of bowel endoscopy.

A major issue is whether registers should be organised on a national basis or on a regional basis. Vasen *et al*³⁸ have reported recently on the success of the national structure in The Netherlands. The register described by Littler and Harper³⁹ is essentially a regional genetics register devoted to a range of inherited cancers. The latter structure is the more

appropriate for a country the size of Britain for, as has been shown in this report, FAPC alone can generate a substantial workload. One useful approach to comparisons between regions and registers is to have a common coding system for family members. Appendix 2 provides a simple two digit coding system which would facilitate comparisons if it were introduced in all registers. The system also provides a basis for recall.

An attractive area for cooperation would be in dietary intervention studies. A recent placebo controlled study has suggested⁴⁰ that the polyp count is reduced in subjects on a diet high in fibre and enriched with vitamins C and E. There is a clear opportunity for such diets to be investigated properly by longitudinal studies of young adults known to be gene carriers but negative on bowel examination.

OVERVIEW

There can be little doubt that molecular genetic analysis will become of major importance in carrier detection in the near future. Our experience has shown, however, that the usual problems of inadequate family structure, substantial recombination fractions, and limited information content with the probes currently available restrict the impact of this approach. Reliable information from flanking markers was obtained in only seven at risk relatives. While DNA probes remain of limited value in carrier identification, information based on age of onset and clinical features is of major value. The 10-fold increase in the number of at risk relatives being screened over the three year period has begun to have an effect on morbidity, with successful prophylactic surgery in several family members who had been lost to follow up or who had been inappropriately discharged. A system of notification is being developed based on the computerised register to ensure that appropriate family members are seen regularly by the surgeon responsible for the care of that family.

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APPENDIX 1 Risk calculation in FAPC pedigrees. Use of Bayes's theorem to combine risk estimates.

Subjects with a parent affected by FAPC or with an affected sib and a parent who died at an early age from bowel cancer have a prior probability of 0.5 or 1 in 2 of developing the disease. If, on examination, they are found to have several bowel adenomata, or they have more than five CHRPEs, or they have other extra-colonic features, such as multiple osteomata and multiple sebaceous cysts, they may be assumed to be gene carriers. If bowel examination is negative, their probability of being a gene carrier is reduced. The degree to which they may be reassured depends on their age and on the local reliability of ophthalmological examination. Thus, if a subject with a CHRPE positive relative (see discussion) is found by an experienced ophthalmologist to have fewer than four CHRPEs and none of these has the pathological features seen in FAPC, the conditional probability of being a gene carrier is 1 in 10.

The second conditional factor is the age at negative examination. Referring to the earlier analysis, negative sigmoidoscopy at 25 years leaves a 1 in 10 chance of being a gene carrier. Molecular genetic analysis should be treated in a similar way. If an

affected parent is heterozygous for the probe YN5-48 and phase is known (that is, family study has established which allele is cosegregating with the APC allele) the demonstration that the consultand has inherited the 'favourable' allele represents a conditional probability of 1 in 20. This is based on the assumption of a 5% crossover rate discussed above. These pieces of information should be combined, according to Bayes's theorem, in the following way.

	Carrier	Non-carrier
Prior probability	1/2	1/2
Conditional probabilities		
Bowel negative at 25 years	1/10	1
Fewer than 4 CHRPE 'dots'	1/10	1
Favourable allele for YN5-48 from a phase known parent	1/20	19/20
Joint probability	1/4000	19/40 or $\frac{1900}{4000}$
Posterior probability	1 or 1/1901	1900

APPENDIX 2 Proposed common coding system for FAPC.

- 0 = At risk
 - 01 Screened every year
 - 02 Screened every two years
 - 03 Screened every three years
 - 04 Screened every four years
 - 05 Screened every five years
 - 06 Screened every ten years
 - 07 Some polyps, not diagnostic, screened every year
 - 08 Not being screened
- 1 = Non-gene carrier
 - 10 Spouse of family member
- 11 Less than 1 in 1000 on age, eye exam, bowel exam, and/or DNA
- 2 = Gene carrier
 - *20 No surgery, no polyps
 - *21 No surgery, polyps present
 - *22 No surgery, inoperable malignancy
 - *23 Colectomy+ileorectal anastomosis
 - 24 Colectomy+ileorectal pouch
 - 25 Panproctocolectomy
 - 26 Other surgery

*Carriers who still need endoscopy.