Screening for familial adenomatous polyposis

When a serious genetic disorder is diagnosed in the family, an immediate question arises: are other family members at risk? Ethical issues arise when DNA technology allows testing of children for a condition which is unlikely to have significant morbidity until later life. Familial adenomatous polyposis (FAP) exemplifies this dilemma. A rational approach to screening requires both an understanding of the natural history of the condition and an acknowledgement of the ethical issues involved.

Natural history and presentation
FAP is the most common of the hereditary polyposis syndromes. Patients typically develop multiple adenomas throughout the large bowel, usually more than 100 and sometimes more than 1000. By the fifth decade colorectal cancer is almost inevitable if colectomy is not performed. Adult patients with FAP are also at increased risk of malignancies of the duodenum, ampulla of Vater, thyroid, and pancreas. Children under 5 years of age may develop hepatoblastoma. Patients with Turcot’s syndrome have FAP associated CNS tumours.

There are three ways in which a patient with FAP may present to the paediatrician.

1. Some will present with colorectal symptoms such as bleeding or diarrhoea.
2. A minority present with extracolonic manifestations (table 1). General paediatricians treating a child with an unusual lesion such as maxillary osteoma or epidermoid skin cysts (Gardner’s syndrome) or a rare tumour such as hepatoblastoma or desmoid tumour should consider the possibility of FAP, particularly if there are multiple tumours or another sibling is affected.
3. Most will be called for screening because of a positive family history.

Colectomy is the only effective therapy that eliminates the inevitable risk of colorectal cancer. In the absence of severe dysplasia, colectomy is usually performed in mid to late teens or early 20s to accommodate work and school schedules. Some clinicians advocate colectomy before puberty so the patient can adapt to life without a colon before adolescence. The greater the number of colorectal adenomas, the greater is the risk of colorectal cancer—so dense polyposis or severe dysplasia might be an indication for earlier colectomy. Almost all adolescents detected by screening are asymptomatic and may find it difficult to contemplate interruptions in their schooling or the effects of surgery on relationships. The surgical option, therefore, must not only be carefully timed but also have low morbidity and excellent functional result. The surgical alternatives are ileorectal anastomosis or restorative proctocolectomy with ileoanal anastomosis (pouch procedure); the former has a lower morbidity but requires regular surveillance of the rectal stump.

Table 1  Extracolonic manifestations of FAP in children and young adults

<table>
<thead>
<tr>
<th>Site</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Osteomas, mandibular and maxillary osteotomy</td>
</tr>
<tr>
<td>Dental abnormalities</td>
<td>Impacted or supernumerary teeth</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>Desmoid tumours</td>
</tr>
<tr>
<td>Eyes</td>
<td>Subcutaneous cysts</td>
</tr>
<tr>
<td>CNS</td>
<td>Congenital hypertrophy of the retinal pigment epithelium</td>
</tr>
<tr>
<td>Adenomas</td>
<td>Glioblastomas, e.g. Turcot’s syndrome</td>
</tr>
<tr>
<td>Carcinomas</td>
<td>Thyroid gland, adrenal gland</td>
</tr>
<tr>
<td>Liver</td>
<td>Hepatoblastoma</td>
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Genetics
The prevalence of FAP is estimated at 1 per 10 000. It is inherited as an autosomal dominant trait with high penetrance but with a variable age of onset. The rate of spontaneous mutations is relatively high (reported as 10–30%).

The gene responsible for FAP, APC (adenomatous polyposis coli), was localised to chromosome 5q21 in the late 1980s. The isolation and characterisation of the APC gene followed. This large gene comprises 15 exons, encoding a protein of 2843 amino acids, exon 15 being the largest (see fig 1). The APC gene appears to be a tumour suppressor gene. Most mutations are small deletions or insertions which result in the production of a truncated APC protein. In FAP, a germline mutation inactivates one of the two APC alleles which underlies the predisposition to adenoma formation.

Mutations are widely distributed throughout the 5’ half of the gene, though two “hot spots” are found at codons 1061 and 1309. These account for around one third of all mutations detected and are associated with a more severe phenotype. Other phenotype-genotype correlations have been observed. For example, a higher density of colonic adenomas is found when mutations are located in the central portion of exon 15. A variant of FAP has been described which is characterised by fewer colonic polyps and a generally milder phenotype, so called attenuated FAP. APC mutations have been described for this condition at the 5’ and 3’ extremes of the gene. These correlations are not absolute and there may be considerable intrafamilial variation, suggesting that there are other factors involved in the pathogenesis of the disease. Some of the phenotypic variability seen in patients cannot be explained by the location of their APC mutation. Environmental factors and other genes—often termed modifier genes—may have critical effects on APC function and disease expression.

The gold standard for genetic testing is seeking the mutation directly from DNA, usually purified from phlebotomy samples. The initial step may often be an RNA protein truncation test or DNA single strand conformation polymorphism analysis. Subsequent direct sequencing/mutation analysis directly detects the exact nature of the APC gene mutation. Once a specific mutation is identified in an affected family member, a restriction enzyme is designed to detect the new base pair sequence. More than 300 different germline mutations have been described and finding the initial mutation may be a formidable task. Families need to be aware that the mutation may only be detected in 60–80% of cases—it is only in these cases that a predictive test can be offered to at risk individuals.

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Screening: genetic and clinical assessments

In order to define which screening protocol is appropriate for a given family, the first step is to determine, where possible, which mutation is present in the FAP affected index case. At this stage, if a mutation cannot be found, the genetic testing is non-informative and it will not be possible to offer predictive testing to asymptomatic at risk relatives. For the 60–80% in which a mutation is detected, at risk relatives can be tested. A negative test is considered accurate in excluding FAP and the subject should be considered to hold an average population risk for the subsequent development of adenomas and cancer. Such genotype negative individuals can be discharged from follow up. The exception to this would be in those patients where the deletion has not be sequenced, but has been excluded by linkage analysis with intragenic markers alone (a less reliable method for determining the risk of carrying the APC gene mutation)—in this circumstance our practice is not to discharge and to consider endoscopic surveillance.

A positive test confirms the diagnosis of FAP and patients should undergo endoscopic assessment. The diagnosis is confirmed by finding polyps at flexible sigmoidoscopy, histologically confirmed as adenomas. (Alternatively, the presence on indirect ophthalmoscopy of more than four pigmented ocular fundus lesions—congenital hypertrophy of the retinal pigment epithelium, carries a 100% positive predictive value, particularly if the lesions are large. The absence of pigmentation, however, is of no predictive value.) At St Mark’s Hospital (London), affected individuals undergo annual flexible sigmoidoscopy from the age of 11–14 years until adenomas are found. Annual flexible sigmoidoscopies should be adequate since there is rectal involvement early in the condition in virtually all patients.

In families in which the genotype is not known, protocols vary—the St Mark’s approach is to perform annual sigmoidoscopy on all first degree relatives until adenomas are found. More frequent assessments should not be necessary, and assessments more than one year apart might impact on attendance for screening, or miss aggressive disease. In addition, from the age of 20 years, colonoscopy with dye spray is performed at five yearly intervals. Figure 2 provides a summary of the St Mark’s screening protocol.

Most gene positive children will have had a full colonoscopy by the age of 16 years to determine polyp density and location, and degree of dysplasia. With this information, and understanding the family situation, the psychosocial and schooling needs of the child, a decision can be made regarding the timing and type of surgery. Further colonoscopies might be performed to reassess the extent of poly-
pisodes if the adolescent wishes to delay surgery, for example, to the age of 18 years, but clinicians and patients should be aware that colonoscopic surveillance alone is not a safe enough method of preventing colorectal malignancy, and has its own complication rate.\textsuperscript{14, 15} It is important that the adolescent becomes familiar with the examinations. Children and adolescents should undergo screening endoscopies in a paediatric gastroenterology unit to ensure that early screening experiences are seen in a positive light as subsequent examinations are dependent on voluntary participation. Therefore, clinicians should consider the benefits of colonoscopy under general anaesthesia in those children who are unlikely to tolerate the procedure, for example, because of young age or learning difficulties.

No patient should undergo screening for FAP without detailed counselling. Expert genetic counselling of newly diagnosed patients and their relatives and the involvement of a clinical geneticist or genetic counsellor is recommended. It is essential that the individual being screened understands the nature of the test and its possible outcomes. Issues such as emotional, family, insurance, and employment implications of a positive result should be discussed prior to testing and there should be a clear protocol for post-test management. Recent evidence shows that many individuals who underwent commercial genetic tests for FAP received inadequate counselling and some had been given poorly interpreted results.\textsuperscript{18}

Timing of screening

The age at which to start screening of children at risk of FAP is a significant issue which requires careful consideration. As already discussed, the disease will usually not present or require treatment before adolescence or adult life. Those children found not to carry the mutation will be relieved to find they do not have FAP and will be spared an infrequent but anxiety provoking annual sigmoidoscopy. For those found to have the mutation, there is the removal of uncertainty and doubt, preparations can be made for the future (for example, surgery), and there will probably be more acceptance of the screening endoscopies. However, early knowledge of the child's disease status may have detrimental effects: it may lead to denial, anger, or anxiety; result in harm to the child's self concept; or even affect relationships within the family.\textsuperscript{17-19} Even if test results are negative, parental anxiety may remain. Many authorities feel that the child should be involved in the decision making process, and the diagnosis be delayed until the child is old enough to contribute to the screening programme.

Our practice for families with a known mutation is to offer genetic screening to first degree relatives from the age of 11 years onwards; at this age we feel the child is more able to understand the consequences of the result. Some children, however, will understand the genetic screening and its consequences at a younger age (for example, 9 years); the maturity of the child and each family situation should be considered individually. Severe dysplasia and even malignancy have been documented in children with FAP under the age of 12 years, although this is rare. Consequently, those children who have gastrointestinal symptoms such as blood loss or diarrhoea or from families in which severe dysplasia or carcinomas have been found at a young age, may undergo screening at an earlier age.\textsuperscript{20} This is particularly so if the family has one of the mutations associated with a severe phenotype, for example, 1309 in exon 15.\textsuperscript{5, 7}

To determine whether the screening protocol described above was appropriate and adequate in preventing malignancy, a retrospective review of the findings at screening sigmoidoscopy of 267 children aged 11–16 years with a first degree relative with FAP over a 50 year period was undertaken at St Mark's Hospital.\textsuperscript{20} Of 123/267 ultimately diagnosed with FAP, only 7/123 (6%) had more than 20 adenomas at screening sigmoidoscopy. No malignancies were identified in this cohort. Histopathology was available from 112/123 colectomy specimens; only four showed severe dysplasia (the precursor to malignant change in the adenoma–carcinoma sequence). All patients found to have severe dysplasia described significant gastrointestinal symptoms in adolescence, including bleeding per rectum and/or diarrhoea. The conclusion from this study was that no evidence was found to support routine genotyping or sigmoidoscopy before age 11 years in children from families with FAP, although testing of children before this age may have a role in those who have symptoms, for example, bleeding and/or diarrhoea.

FUTURE ADVANCES

A change in the criteria for defining the optimal age for screening for FAP may, however, be on the horizon if studies into chemoprevention currently underway are found to be successful. Non-steroidal anti-inflammatory drugs (NSAIDs) may be protective against colon cancer,\textsuperscript{21} with several trials showing regression of adenomas using the NSAID sulindac.\textsuperscript{22, 23} Widespread use of sulindac has been limited by concerns regarding gastrointestinal side effects with prolonged administration and case reports of rectal cancer developing treatment.\textsuperscript{24} The CAPP (Concerted Action for Polyposis Prevention) study is currently assessing the effectiveness of intervention strategies such as the administration of aspirin and dietary manipulations with resistant starch.\textsuperscript{25} Clinical trials using selective COX-2 inhibitors have reported a reduction in the number of colorectal polyps.\textsuperscript{26} This agent, and also the non-cyclooxygenase metabolite of sulindac, sulone-sulindac, may have a role prior to surgery in adolescents and, as such, are the subject of small scale trials in a paediatric setting.

Conclusions

Genetic testing is available for many children at risk of FAP and thus it is possible to start screening for the condition at a much earlier age. There are clear advantages to knowing whether a child will develop the phenotype of FAP, but inappropriately timed gene testing may be unnecessary and detrimental. It has been our practice to delay routine screening until the age of 11–14 years. This practice allows the child to be involved at the start of a process which may last several years; thus far, over 250 children have been screened in this manner, and no cases have developed malignant changes prior to colectomy. The timing of screening is a decision to be shared with the family on an individual basis—some children are ready at an earlier age. In symptomatic individuals early screening, and in particular endoscopy, is indicated. In the future, if chemopreventive agents can be shown to slow the development of adenomas, routine earlier screening may become indicated.

In response to a parent’s request to have their child tested for FAP, it is important to determine what question needs to be answered—is the test purely to put the parents’ mind at rest or will it affect the child’s management? Childhood testing for polyposis syndromes should be carefully timed and appropriately interpreted.

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