

Brief papers

Familial adenomatous polyposis in a 5 year old child: a clinical, pathological, and molecular genetic study

S Distante, S Nasioulas, G R Somers, D J S Cameron, M A Young, S M Forrest, R J M Gardner

Abstract

A girl aged 5 years 8 months presented with rectal bleeding; her father had had familial adenomatous polyposis (FAP) and a colectomy at the age of 23. Endoscopy showed extensive polyposis and she had a colectomy. The proband and her father had the common codon 1309 5 bp deletion APC mutation. This mutation predisposes to early onset of FAP, and consideration needs to be given to having molecular testing of at risk members of these families done in childhood.

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Key words: familial adenomatous polyposis; codon 1309 mutation.

The APC gene causing familial adenomatous polyposis (FAP) was mapped in 1987¹² and cloned in 1991.³⁴ Several mutations have been defined.⁵⁻¹⁰ Two common mutations, at codons 1061 and 1309, account for about 20% and 9% of the total respectively.⁹ The latter mutation comprises a 5 bp deletion extending from the last base of codon 1309 to the first base of codon 1311; for simplicity, we refer to this as the "codon 1309" APC mutation. Most APC mutations are frameshifts which produce a premature stop codon, with consequent truncation of the protein product. A genotypic-phenotypic correlation has been proposed, with longer truncated products (mutations in codon 1309 and beyond) associated with more severe and earlier onset disease and the presence of congenital hypertrophy of the retinal pigmented epithelium (CHRPE).¹¹ Shorter truncated products cause a milder disease, and a very short truncated product leads to "attenuated polyposis".¹²¹³ We describe a family with the codon 1309 mutation, with onset in young adulthood and young childhood respectively in the father and daughter, and we review the molecular genetics of childhood polyposis.

Case report

The proband presented initially at the age of 5 years 8 months with rectal bleeding and

frequent stools. The clinical pattern suggested bacterial infection, but no recognised pathogens were isolated. Her symptoms settled within a few days, but rectal bleeding recurred one month later in the absence of other symptoms. She had no previous gastrointestinal or extra-intestinal symptoms or signs. Colonoscopy showed hundreds of sessile polyps of varying sizes, up to about 10 mm in diameter. There was no unequivocal observation of a polyp in the distal ileum. On gastro-duodenoscopy there were two small sessile polyps seen in the second part of the duodenum. Follow through barium contrast x rays did not show any additional polyps in the small intestine. She underwent a total proctocolectomy and ileal pull through procedure with a temporary loop ileostomy which was subsequently closed.

The resected colon contained innumerable polyps, measuring up to 9 mm in diameter. Most were sessile, although a small number were slightly pedunculated. There were occasional small areas of ulceration. The rectum contained relatively few polyps, with normal mucosa in between. Histology of both colonic and duodenal polyps showed many adenomatous polyps with no extension beyond the muscularis mucosae.

Subsequent endoscopic surveillance at the age of 6 years 10 months showed small sessile polyps in the stomach (2), pylorus (1), second part of the duodenum (2), and first part of the jejunum (1), all too small to be removed endoscopically; there were none in the terminal ileum.

The girl's father, himself an only child, was diagnosed with FAP at the age of 23 years, and he had total colectomy with permanent ileostomy. We had planned an ophthalmological assessment as part of the family study; however, he became ill with an extremely aggressive pulmonary infiltrative condition and died within a few weeks, at the age of 45, the diagnosis being lymphoma. His father was said to have been diagnosed with polyposis in his twenties; he had had a permanent ileostomy and died at 51 years of an apparently unrelated cause. The girl's paternal great grandfather was said to have died of bowel cancer in his eighties.

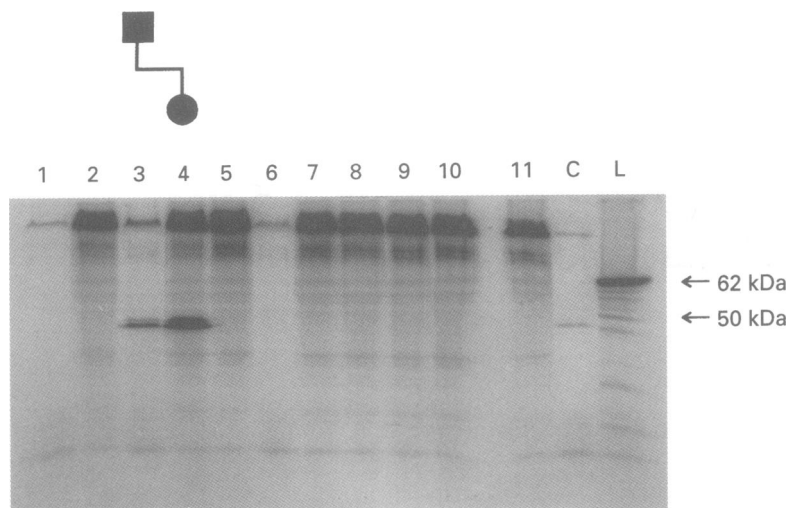
The Murdoch
Institute, Royal
Children's Hospital,
Flemington Road,
Parkville 3052,
Melbourne, Australia
S Distante
S Nasioulas
S M Forrest
M A Young
R J M Gardner

Department of
Anatomical Pathology,
Royal Children's
Hospital,
Melbourne 3052,
Australia
G R Somers

Department of
Gastroenterology,
Royal Children's
Hospital,
Melbourne 3052,
Australia
D J S Cameron

Correspondence to:
Dr Gardner.

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Protein products in the father (lane 3) and child (lane 4) from the *in vitro* translation assay to detect protein truncation. Lane C is a known codon 1309 mutation. Lanes 1–2 and 5–11 are other FAP cases. L = size ladder.

No extracolonic features were anecdotally reported in the father, grandfather, or great grandfather. Her older brother underwent gastroduodenoscopy and ileocolonoscopy aged 12 years 4 months; no polyps or other abnormalities were seen.

Molecular studies

Primers used for amplification of a fragment of exon 15 (“fragment 3”, comprising codons 1029–1701) were those designed by van der Luijt *et al.*¹⁴ Polymerase chain reaction (PCR) was done under standard conditions. The final concentration of magnesium chloride was 1.5 mmol/l MgCl₂ and the annealing temperature 56°C. PCR conditions were denaturation at 95°C for one minute, annealing temperature for one minute, and extension at 72°C for two minutes, for a total of 40 cycles. The protein truncation test (PTT) was based on the method of Roest *et al.*¹⁵ using the TnT T7 reticulocyte system (Promega). Incorporation of ³⁵S methionine was used to detect the translation protein products. Separation was done on a 14% SDS-polyacrylamide gel which was fixed and then dried and exposed to x ray film.

Testing of “fragment 3” by the protein truncation test (PTT) showed a truncated protein of around 50 kDa in size, in the samples from both the child and her father. A patient with a known codon 1309 mutation was used as a control and gave a truncated protein product of the same size (figure). The region encompassing the mutation was amplified from genomic DNA using the primers of Ando *et al.*¹⁶, and the child and father showed the 5 bp deletion (results not shown).

Discussion

It is rare for familial adenomatous polyposis to present in childhood. Polyps may begin to form at an early age,¹⁷ but sufficient growth to be symptomatic or to warrant consideration of

prophylactic colectomy does not usually occur until late adolescence or adulthood. While diagnosis by surveillance colonoscopy owing to positive family history is being increasingly described,¹⁸ actual clinical presentation in the paediatric age group is very rare. (It is necessary to draw a distinction between FAP in a juvenile and the separate entity of juvenile polyposis.¹⁹ The coexistence of juvenile and adenomatous polyps has been the subject of several recent reviews^{20–23} and presents a diagnostic challenge.)

Abramson¹⁷ published a remarkable review of childhood polyposis up to the 1960s. He was able to find two reports from the 1890s and 32 from this century, presenting from infancy through to 13 years of age. His pathological description of “multiple polyposis” with family history translates into the more modern term of FAP, and he did account for the distinction from other types of polyp. Peck *et al.*,²⁴ in 1972, recorded a total of 11 persons with FAP aged 16 years and under who had bowel cancer; six of these were children aged 12 and under. Possibly the youngest ever reported case is that of LeFevre and Jacques²⁵ in 1951, a 4 month old infant with symptomatic prolapsing polyposis which led to death from intussusception and gangrene.

Thereafter, there have not been many reports of FAP in childhood. Bülow²⁶ reviewed the Danish Polyposis Register up to 1982, and recorded an age range for onset of bowel symptoms of 2 to 73 years. Chow *et al.*¹⁹ recorded the case of a 12 year old presenting with scalp epidermoid cysts and with multiple polyps, whose sibs (aged 11 and 13) and mother also had Gardner’s syndrome. Ruttenberg *et al.*²⁷ reported an 8 year old with FAP presenting with acute abdominal pain in whom colonoscopy showed over 100 polyps, and one large pedunculated polyp (3.5 cm) had a significant degree of dysplasia.

Since the discovery of the APC gene, it has been recognised that patients with the codon 1309 mutation, or with mutations 3’ of this point, generally have a more severe disease phenotype (defined as the presence of thousands of polyps rather than hundreds, age of onset before 12 years, or advanced neoplastic disease before 30 years).¹¹ In the small number of childhood cases (12 years of age and under) so far reported having had mutational analysis, 10 have had the codon 1309 mutation,^{11 28 29} and five have had mutations more 3’ in the gene, within codons 1445 to 1578.³⁰ With respect to the codon 1309 mutation, Gayther *et al.*¹¹ list two 7 year olds, a 9 year old, and a 12 year old presenting symptomatically or with cancer. The two children in the report of Caspari *et al.*²⁸ presented with intestinal bleeding at the ages of 4 and 6 years, and had subtotal colectomies at the ages of 7 and 8 years, respectively. Presciuttini *et al.*²⁹ recorded an 8 year old and a 10 year old in one family with the codon 1309 mutation, and an 8 year old and a 13 year old in another; they make the case that anticipation characterises the transmission of this and some other APC alleles. The child we report here with the codon 1309

mutation presented at the age of 5 years 8 months, and had a severe degree of colonic polyposis and upper gastrointestinal tract involvement; her family history is not inconsistent with the possibility of anticipation.

Another mutation associated with early onset is the 13 bp deletion from nucleotides 2504–2516 causing a stop codon at position 835, recorded in a 14 year old.²⁹ Presciuttini *et al*,²⁹ noting the more 5' location of this mutation, proposed a revision of the model of a "linear" molecular-clinical correlation, and suggest that mutations at particular critical points, rather than simply according to distance along the gene, cause more aggressive disease; the case of Eccles *et al*,³¹ a girl who died of colon cancer aged 16 years and had a de novo mutation at codon 1179, provides further illustration. Caspari *et al*³⁰ expanded on this theme, and showed that persons with mutations beyond codon 1444 almost always have desmoid tumours, osteomas, epidermoid cysts, and polyps of the upper gastrointestinal tract, but no CHRPEs. In fact, their only cases with beyond 1444 mutations who did not have desmoids were children (ages 4, 5, and 10 years); one 14 year old had a desmoid tumour present since birth. Some Turcot's syndrome (colorectal polyposis plus primary brain tumour) results from APC mutation, and with this entity, in contrast, the coexistence of brain tumour seems unrelated to the site of mutation.³²

Given the molecular-clinical correlation, is it appropriate to provide specifically tailored advice to families with "early onset mutations"? While normal practice may be to offer testing to young persons at risk for FAP mutations during early teenage (the time at which colonoscopy would otherwise have been proposed), in those in whose family the mutation is at codon 835, 1309, or beyond 1444, or is otherwise a known early onset mutation, a younger age may be advisable. Our patient's older brother, aged 12, had already had normal endoscopy, as noted above, and our plan was to make mutation testing available to him, using a modified version of the protocol we apply to adult predictive testing. In preliminary discussion, he appeared to have a good understanding of the issues. His father's recent death from a presumed unrelated malignancy led us to defer the matter. The British Clinical Genetics Society has addressed the question of predictive testing in children, taking cognisance of such matters as the child's future autonomy and confidentiality.³³ Of 49 geneticists questioned, 16 (33%) would not test a 5 year old at risk for FAP whose parents wanted to know the child's genetic status. Clayton³⁴ commented that there is the possibility of conflict with parents, as physicians come increasingly to act as advocates for what they see as the child's interests, but notes further that "children are generally ill-served if their parents feel they have not been listened to"; and the Genetic Interest Group in the UK has enunciated the following principle: "After suitable counselling, parents have the right to make an informed choice about whether or not to have their children tested for carrier status. Ideally, children

should only be tested when of an age to be involved in the decision".³⁵ In the specific case of an "early onset FAP mutation", we propose that a more liberal view may be warranted, both in response to justifiable parental concern, and for medical management of the child's condition, because we do not at present know the risk for progression to malignant change before adolescence.

Note added in proof

The brother, now 13 years old, did present for predictive testing. We were impressed with his intelligent and articulate appreciation of the issues. He did not have his father's APC mutation.

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