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Case Report Open Access

Polyposis Caused by Low APC Mosaicism

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Abstract

Purpose: To present a patient with familial adenomatous polyposis (FAP) caused by a low level of somatic mosaicism.

Case description: A twenty-one year old female presented with rectal bleeding and abdominal pain. She underwent a colonoscopy and esophagogastroduodenoscopy which revealed extensive polyposis. There was no family history of polyps or early onset colon cancer in her family.

Methodology: Next-generation sequencing (NGS) analysis was performed using the ColoSeqTM panel on DNA extracted from both peripheral blood lymphocytes and colonic polyps. RESULTS: Molecular analysis detected the p.E1408X deleterious mutation in the APC gene in in 12 of 276 (4%) reads of the DNA in the peripheral blood leukocytes and in 30% of the DNA from colonic polyps.

Conclusion: We report that low level of 4% APC mosaicism led to florid polyposis. Our report highlights the power of deep next-generation sequencing to identify mosaic mutations that are missed by traditional approaches. Though somatic APC mosaicism has previously been reported to cause polyposis syndrome in a few cases, it has been underestimated as a cause of polyposis coli. This case should reinforce the need to search for mosaicism in all patients with a personal history of polyposis and no family history.

Keywords: APC; ColoSeqTM panel; FAP; Mosaicism; NGS

Abbreviations: APC: Adenomatous Polyposis Coli; CRC: Colorectal Cancer; FAP: Familial Adenomatous Polyposis; MAP: MUTYH-Associated Adenomatous Polyposis; NGS: Next-Generation Sequencing

Introduction

Familial adenomatous polyposis (FAP) (OMIM #175100) is an autosomal dominant disorder that leads to the development of hundreds of colonic adenomatous polyps and eventually, if untreated, colorectal cancer. The diagnosis of FAP generally requires the presence of a genetic mutation in the adenomatous polyposis coli (APC) gene [1]. Attenuated familial adenomatous polyposis (AFAP), which often has a fewer number of colonic polyps is also caused by mutated APC. A variant form of FAP is MUTYH-associated adenomatous polyposis (MAP), which results from a mutation in the MUTYH gene. A 2015 American College of Gastroenterology guideline recommended that treatment is determined by clinical symptoms even in the absence of a positive genetic test result. They recommend genetic testing for mutations in the APC and MUTYH gene in patients with suspected adenomatous polyposis syndromes [2]. The recommendations also state that if testing for APC and MUTYH is negative, yet the clinical suspicion for FAP is still high, other potential culprit genes should be tested.

In a large cross-sectional study, APC mutations were found in 80% (95% CI 71%–87%) of individuals with more than 1,000 adenomas, 56% (95% CI 54%–59%) with 100–999 adenomas, 10% (95% CI 9%–11%) with 20–99 adenomas, and 5% (95% CI 4%–7%) with 10–19 adenomas [3]. Pathogenic mutations are not detected in some FAP cases by conventional direct sequencing owing to several reasons, including; (i) The region of testing is often restricted to 5'-half in the coding region and does not usually include the 3'-half, promoter region, or the 5'- or 3'-UTR. (ii) Structural alterations comprising large deletions/insertions and inversions are hard to identify by the conventional sequencing method. (iii) Some cases of adenomatous polyposis are caused by mutations in other genes such as MUTYH, POLD1 and POLE [2,3] (iv) Some FAP cases are caused by somatic mosaicism of APC [4].

Large-scale genome sequencing, also known as next-generation sequencing (NGS), is applicable to various clinical situations including the detection of rare hereditary mutations, individualized therapy, pharmacogenomics, preconception/prenatal screening and population screening for disease risk. NGS allows for simultaneous deep sequencing of multiple genes and has been shown to improve mutation detection in genetic diseases [5]. In addition, NGS is sensitive enough to detect low level mosaicism, while the Saenger sequencing method for genetic testing is not sensitive enough to detect genetic defects when the rates of mosaicism may be low.

Genetic mosaicism exists when a person is composed of multiple genotypes [6]. Few case reports and studies have demonstrated that mosaicism is present in a subset of FAP patients harboring de novo germline mutation of APC, but mosaicism among APC carriers may have been underestimated [7,8]. Mosaicism was detected in 4% of 242 patients with FAP [9]. A 2015 case report showed 12% of APC mosaicism in a patient with AFAP, using NGS analysis after Saenger

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sequencing did not reveal any mutations [8]. However mosaicism is not routinely looked at in patients with sporadic polyposis.

We present a young patient with FAP caused by a low level of 4% APC somatic mosaicism in the blood and a higher level of mosaicism in the polyp.

Case Presentation

A twenty-one year old female presented to the hospital with rectal bleeding and abdominal pain. The patient underwent a colonoscopy and esophagogastroduodenoscopy, which revealed extensive polyposis of the recto-sigmoid junction and distal sigmoid, extensive polyposis of the proximal right colon and cecum and scattered polyps in the left and transverse colon. (Figure 1) The rectum was essentially spared aside from two small pedunculated polyps. The stomach and duodenum, including the papilla, were normal. In preparation for recto-sigmoid sparing surgery, more than sixty polyps were removed from the recto-sigmoid junction and distal sigmoid. The polyps were found to be tubular adenomas. She then underwent laparoscopic total intra-abdominal colectomy.

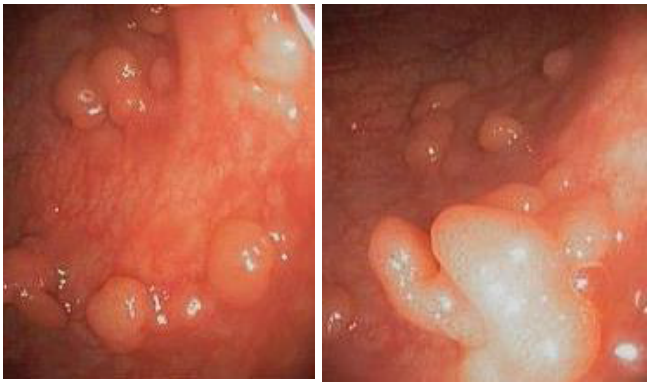

Figure 1: Colonic polyps along the colon.

The patient had no extra-colonic signs of FAP. Family history was not indicative of a polyposis syndrome, as although her maternal grandmother was diagnosed with colon cancer at age seventy-six, there was no other family history of polyps or colon cancer (Figure 2).

The patient signed an informed consent for genetic analysis. NGS analysis was performed using the ColoSeqTM panel on DNA extracted from both peripheral blood lymphocytes and from few colonic polyps [10]. DNA from few adenomas was merged. Molecular analysis detected the p.E1408X deleterious mutation in the APC gene in 12 of 276 (4%) reads of the DNA in the peripheral blood and in 30% of the DNA from colonic polyps (Figure 3).

Discussion

Our patient had typical gastrointestinal manifestations of dozens of colonic adenomas. Though she did not have extra-colonic manifestations and was the only member of her family who had polyposis, she was highly suspected of having FAP. NGS analysis showed that low levels of only 4% APC mosaicism in the peripheral blood lead to florid polyposis. Given the low level of mosaicism, we also tested DNA extracted from a polyp, and found a higher level of mosaicism (30%) in the affected tissue.

Peripheral blood originates from mesoderm, hair follicles and buccal mucosa from ectoderm, and gastric and colonic mucosa from endoderm. Therefore, the mutation should have occurred before the separation of these three layers. The risk of transmission of the patient's polyposis to her offspring is probably less than 50%.

In up to 25% of index patients with FAP, a de novo APC mutation is identified [4,9]. Twenty percent of FAP patients are considered sporadic or simplex cases, as they do not have any family history of polyposis.

In disorders with a relatively high frequency of new mutations, somatic mosaicism is frequently described [11]. Thus, given the relatively high frequency of de novo APC mutations, somatic mosaicism may account for a substantial portion of sporadic polyposis coli patients; However, mosaicism has previously been reported in only a few cases of FAP or AFAP [7,8].

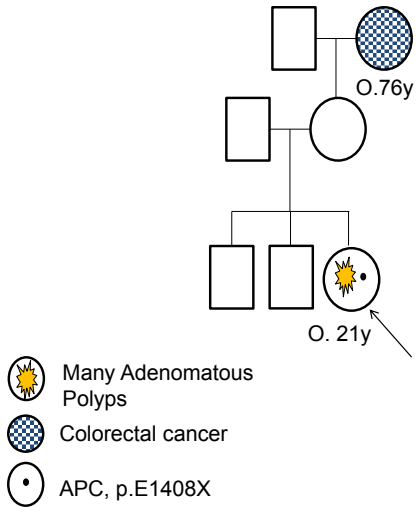

Figure 2: Pedigree of the affected patient.

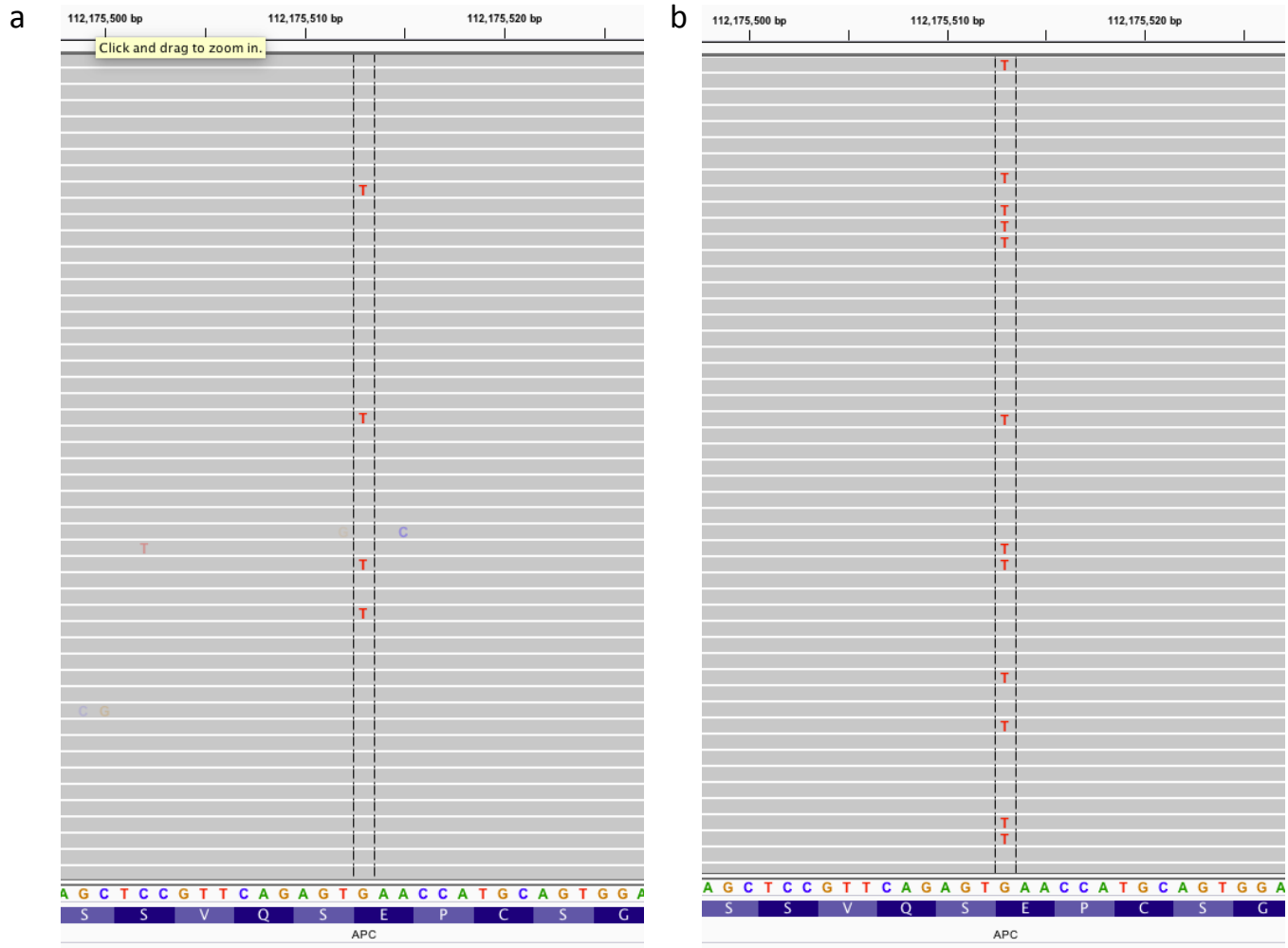

Figure 3: NGS molecular analysis detected the p.E1408X deleterious mutation in the APC gene in 4% of reads from peripheral blood (a) and in 30% of reads from colonic polyps (b).

Hes et al [9] reported that 4% of 242 FAP index patients or 21% of apparently sporadic FAP patients had APC mosaicism. The actual numbers mosaicism may be much higher as low levels of mosaicism is not detected by the conventional Saenger technique and searching for mosaicism is not part of the routine genetic work-up. More-over, many of the laboratories who use NGS do not report of low levels of mosaicism.

Our case demonstrates that even a low level of APC mosaicism in the blood can lead to typical manifestations of a florid polyposis. Thus, it reinforces the need for NGS analysis in all patients with sporadic polyposis and no identified germ-line mutation by traditional less sensitive approaches.

Ssequencing by the Saenger method is still considered the gold standard of genetic testing for FAP. Application of NGS for patients with polyposis may increase the detection of APC mosaicism in sporadic cases, perhaps identifying those patients with a milder phenotype. One may also consider NGS testing of the polyp DNA if diagnosis is in doubt, or in cases with low levels mosaicism.

We suggest that sequencing by NGS should replace the screening strategies for polyposis, mainly in sporadic cases, not only because it can be directed to several candidate genes, but it also because it can detect mosaicism.

The clinical importance of identifying further genetic mutations is clear as mutational mosaicism has relevance to cancer risk and cancer prevention. In FAP, genetic diagnosis is useful for decisions regarding surveillance and personalized treatment of patients, and may be applied for the pre-symptomatic or even pre-gestational and prenatal diagnosis of their children.

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Conflict of Interest

All the authors declare no conflict of interest.

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