Case Report

Novel Missense Mutation at Codon 2774 (C.8321 G>A) p.S2774N of APC Gene in a Denovo Case of Familial Adenomatous Polyposis

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Abstract

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease caused by germline mutation in Adenomatous Polyposis Coli (APC) gene. FAP accounts less than 1% of all colorectal cancers incidence. Patients generally present hundreds to thousands of adenomas in colon and rectum and develop colorectal cancer by age 35 – 40 if left untreated. A milder form of FAP with fewer numbers of polyps (< 100) is Attenuated FAP (AFAP) and in comparison with classical FAP, it usually diagnosed at an older age. Approximately 15% – 20% of FAP patients are "de novo" cases without any family history of the disease and novel APC mutations account for approximately 25% of FAP cases. In our study, we reported a novel missense mutation at the APC gene in a denovo patient with AFAP like phenotype.

Keywords: AFAP, APC, denovo, new mutation

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Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease caused by germline mutations in APC gene (5q21-q22; OMIM#175100).[1] Less than 1% of all colorectal cancers accounted for FAP incidence. The APC gene is a tumor suppressor gene located on the short arm of chromosome 5 (5q21-22).[2] APC spans a region of 108,353bp (NC_000005) and the protein contains 2843 amino acids with molecular weight of 310 kDa (NCBI# NP_000029). APC protein has several functions including cell division, migration, cell adhesion and signal transduction.[1] The main function of APC is to regulate β-catenin protein level. In the absence of normal APC, β-catenin protein is accumulated in cytoplasm and via activation of other transcription factors including Tcf it leads to uncontrolled cell proliferation and progression.[2] Truncation protein is the main product of the majority of germline mutations in APC which is the result of nonsense or frameshift mutations.[3] In FAP patients hundreds to thousands of adenomatous polyps develop in colon. A milder form of FAP termed as attenuated FAP (AFAP), presents fewer than 100 polyps and has later onset.[4] The colorectal cancer (CRC) is the inevitable consequence of FAP if the condition is left untreated. Approximately 15% – 20% of patients are considered as "de novo" cases without any family history of the disease.[5] Interestingly, 1 in 8000 to 1 in 10000 births are reported to be de novo cases.[6] In this study we reported a novel missense mutation at APC gene in a denovo patient with attenuated familial adenomatous polyposis in Iran.

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Case Presentation

A 11-year old Iranian teenage girl referred to Gastroenterology and liver disease Research Institute, Taleghani hospital with abdominal pain, diarrhea and anemia. After primary evaluation, family pedigree was drawn (Figure 1) and no family history of colon cancer or other malignancies were detected in the first relative of the patient. Colonoscopy was performed and the report showed multiple 4mm and 5mm polyps in rectosigmoid and 5-10mm polyps in descending colon. Multiple polyps (>10) was also observed in ascending colon as well (Figure 2). Pathology report revealed that rectosigmoid polyps were tubular adenoma with low grade dysplasia (Figure 3). Descending biopsy was confirmed as serrated adenoma. Upper endoscopy showed that patient was positive for H.pylori infection and moderate chronic gastritis was also observed. Due to early presentation of multiple tubular adenomas, the case was considered as AFAP like phenotype. Thus, we scanned the APC coding region and we found adenine to guanine transversion missense mutation at codon 2774 (c.8321 G>A) p.S2774N (Figure 4). We searched Leiden Open Variation Database (LOVD) and we didn't find any previous reported variation at this codon. Based on our finding, this mutation was a novel variant. First degree relatives (FDR) of the patient (both parents and brother of the patient) proceeded genetic testing and underwent colonoscopy. In the colonoscopy, we didn't find any lesions or polyps and they were negative for malignancy. Scanning the APC gene in FDR revealed that they were negative for mutation at exon 15 of APC gene. Therefore, this case without any history of cancer in her family and novel missense mutation at codon 2774 (c.8321 G>A) p.S2774N exon 15 of the APC gene was considered as a denovo case.

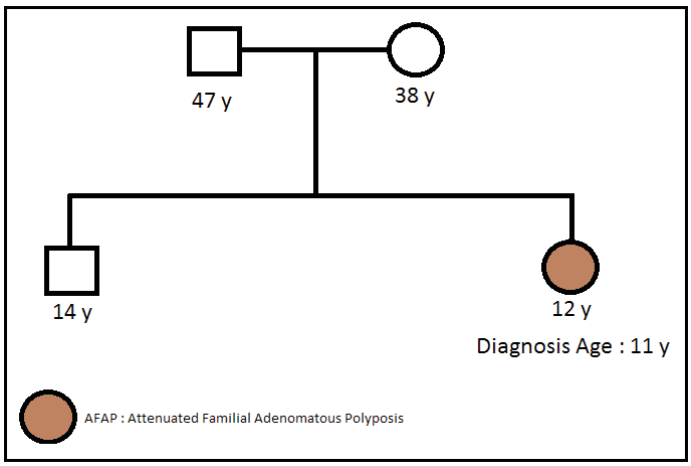

Figure 1. No family history of colorectal cancer or other malignancies identified in the first relative of the patient.

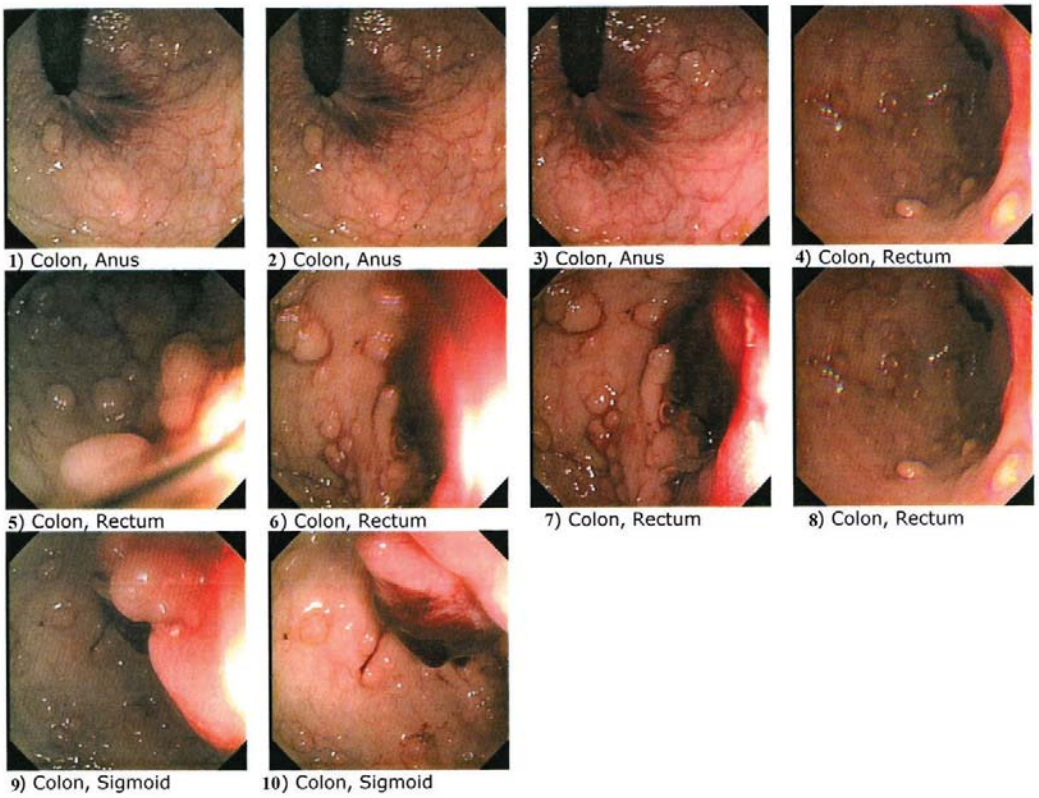

Figure 2. In colonoscopy, multiple polyps <100 were detected in rectum, sigmoid and ascending colon.

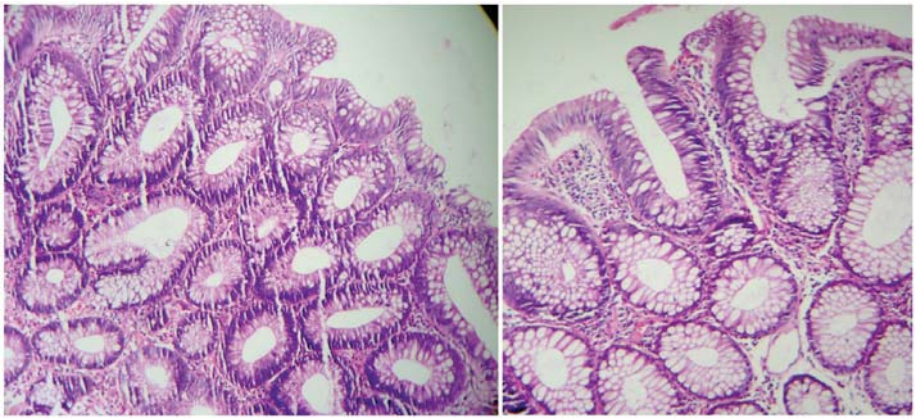

Figure 3. The pathological diagnosis of the rectosigmoid polyp was tubular adenoma with low grade dysplasia.

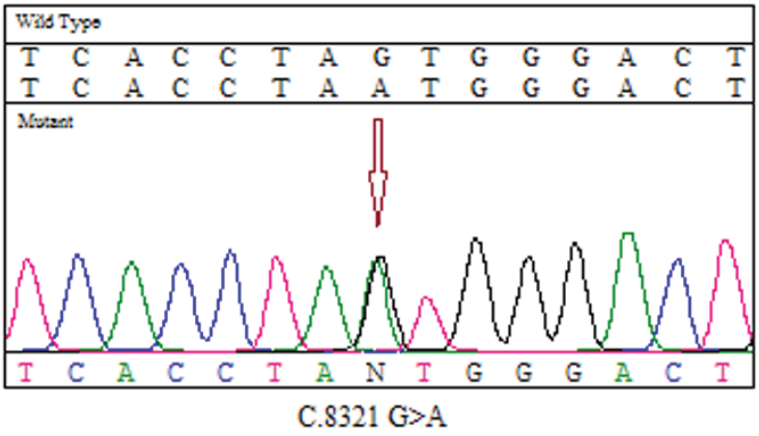

Figure 4. Adenine to guanine transversion missense mutation at codon 2774 (c.8321 G>A) p.S2774N.

Discussion

AFAP patients develop 10 to 100 adenomatous polyps throughout the colon and In comparison with classical FAP patients, this phenotype usually diagnosed at a later age.[4]

The base excision repair (BER) gene MUTYH is another gene identified in FAP and AFAP like patients.[7,8] AFAP Patients usually harbor mutation at 5´ (codons 78 – 167) and 3´ (codons 1581 – 3843) regions of the APC gene.[9] The diagnosis criteria for AFAP patients is detecting fewer than 100 colonic adenomatous polyps (10 – 99) in patient or an individual with 100 or more polyps presented at an older age with a family history of multiple adenomatous polyps.[10] De novo mutation at APC gene is detected in 20% – 25% of FAP patients.[6] Somatic APC mosaicism also accounts for 10% to 15% of cases with de novo mutations.[5,11] This high frequency incidence rate is more likely in cases with a novel APC mutation. In our previous study we identified four familial frameshift mutation including two members of a family with 5 bp deletion (c.3927_3931delAAAGA) and TA deletion at codon 849 (c.2547_2548delTA p.Asp849fsX62) in two siblings in another family.[12] Germline APC mutation and mosaicism in FAP patients also reported in several previous studies.[13,14] Three missense mutations in APC gene are involved in amino acid substitutions and contributed to CRC risk including D1822V, E1317Q, and I1307K.[15] It has been suggested that 5% – 10% of Ashkenazi Jews harbor the p.I1307K polymorphism worldwide.[16,17] A meta-analysis by Jing Liang ,et al. reported a small association between the APC E1317Q polymorphism and colorectal cancer susceptibility,[18] whereas, they found that Ashkenazi Jews who carried the I1307K variant were at a significantly increased risk for colorectal cancer (odds ratio of 2.17, 95% confidence interval: 1.64, 2.86). In our study which is the first report of denovo AFAP case with novel mutation in APC gene in Iranian population, we detected a guanine to adenine transition missense mutation at codon 2774 (c.8321 G>A) p.S2774N, which wasn't reported in any studies previously. Another valuable paper by Ripa, et al. in 2002 reported that among 15 families with novel APC mutation, 10 families presented parental origin of the denovo mutations. Based on their study, they suggested that germline mutation at APC gene mostly results in meiosis division than in premiotic events.[19] Denovo mutation in APC gene was also reported in Hadjisavvas, et al. study. They revealed three truncating mutations at exon 15 of the APC gene including putative 3927del (5bp deletion, c.3927_3931delAAAGA) frame shift mutation. This mutation observed in a patient without any family history of the diseases and represented as a denovo case.[20] They didn't report the frequency of mosaicism in their cases. however, in study of 242 FAP patients, Hes FJ, et al. reported a total of 48 sporadic cases presented with the mosaicism in APC.[11] In line of our study Stec, et al. demonstrated a denovo case of a 25-year old female with familial adenomatous polyposis and novel mutation at codon 953 (2797 –2800 delAACA) of the APC gene.[21] Risk of CRC is well characterized in families with adenomatous polyps.[9] However, the risk for AFAP individuals especially in Iranian population is poorly identified. Thus, there is an urgent need to clarify the underlying mechanisms of AFAP development in Iranian patients. Moreover, the evaluation of the APC mRNA expression level in denovo cases and in patients with missense mutation would be very informative and enlarging the sample size would help us to gain a better evaluation of the role of denovo mutation in Iranian patients with FAP. Thus, we would be able to set a better screening strategy for such patients. In conclusion, we reported a novel missense mutation at codon 2774 (c.8321 G>A) p.S2774N in a 11-year-old patient with multiple tubular adenoma in ascending and rectum. Incidence of missense APC mutations accounts for a significant number of AFAP and FAP patients. In order to get a precise understanding of novel missense mutation in AFAP like phenotype patients, we need to enlarge our sample size. Further meta-analysis might be helpful to determine the association in this region of APC and related phenotypes.

Conflict of interest

There are no conflicts of interest in the authorships to declare.

Acknowledgments

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