Attenuated adenomatous polyposis with MSH6 variation: two case reports

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Case Report

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Abstract

**Background:** Adenomatous polyposis (AP) is a genetic disorder characterized by the occurrence of numerous adenomatous polyps in the colon and rectum and can be classified into classical AP (CAP) and attenuated AP (AAP). AAP is diagnosed when the number of observed adenomas is between 10 and 99. The detection of AAP is significantly increasing mainly due to the improvement of the imaging technique and application of the screening program for colorectal cancer detection. Currently, the germline variations of the *APC* and *MUTYH* genes are reported as the main cause of CAP. However, the underlying genetic basis of AAP is not well understood. In this study, we report two cases of AAP with *MSH6* variations.

**Case reports:** The two patients had multiple colon polyps and were diagnosed with AAP. The two received genetic consultation; and, for follow-up purposes, both patients agreed to be tested for an underlying genetic condition through next generation sequencing (NGS). Germline *MSH6* variations were detected in both patients.

**Conclusion:** Minor portion of AAP can cause by genetic mutation in *MSH6*, and further research is needed.

Introduction

Adenomatous polyposis (AP) is a genetic disorder characterized by occurrence of numerous adenomatous polyps in the colon and rectum [1]. Adenomatous polyposis is classified as classical AP (CAP) and attenuated AP (AAP) according to the number of adenomas [1]. CAP is diagnosed when more than 100 adenomas are present; AAP is diagnosed if the number of adenomas is between 10 and 99 [2]. An adenoma is a benign tumor. However, an adenoma is considered to be a precursor of colorectal carcinoma (CRC); these polyps can progress into cancer if untreated [3]. Therefore, the presence of AP is treated as a cancer risk syndrome with the risk of developing CRC ranging from 40–80% based on the severity of the polyposis [1]. Currently, a germline heterozygous truncating variation of the tumor suppressor gene *APC* is considered to be the main cause of CAP [1]. In addition, germline bi-allelic variations of the *MUTYH* gene have been reported to contribute to the development of CAP [1]. However, variations of *APC* and *MUTYH* are the cause of AAP in only 10–20% of cases [1]. The *MSH6* gene functions in DNA mismatch repair [4]. Variation of the *MSH6* gene leads to dysfunction of DNA mismatch repair and is associated with Lynch syndrome [5]. Although *MSH6* variation has been reported in serrated polyposis [6], this genetic variation has not been reported in AAP. In this study, we report two cases of AAP with *MSH6* variation.

Case presentation

Case 1
A 50-year-old female presented for colonoscopy as part of a medical examination program at a local hospital. More than 20 polyps and a 2 cm mass at the sigmoid colon were identified. The patient was referred to Jeonbuk National University Hospital. After admission, computed tomography was performed, and 2 cm wall thickening of the sigmoid colon was diagnosed. Colonoscopy was also performed, and the sigmoid colon mass with multiple polyps is shown (Figure 1A). Computed tomography of the other sites showed no metastatic lesions. The sigmoid colon mass was biopsied and diagnosed as adenocarcinoma. The patient had more than 20 colon polyps, suggesting AAP. Since there was sigmoid colon cancer along with AAP, total colectomy was performed. The sigmoid colon mass was diagnosed as moderately differentiated adenocarcinoma that had metastasized to one regional lymph node (pT2N1a) (Figure 1B). The colon polyps were diagnosed as tubular adenomas (Figure 1C and 1D).

Based on the presence of multiple polyps in the colon, we recommended genetic analysis to the patient. The patient consented, and we performed next generation sequencing (NGS) with an Oncomine Comprehensive Assay Plus (Thermo Fisher Scientific, Waltham, MA, USA) panel. The result revealed variation in the \textit{MSH6} gene (c.3163G>A, p.Ala1055Thr). No variation was present in the \textit{APC} gene. Since the findings were consistent with AAP, normal tissue was also sequenced through NGS. The identical \textit{MSH6} gene variant (c.3163G>A, p.Ala1055Thr) was detected in the normal tissue. Based on these findings, we concluded that the \textit{MSH6} gene (c.3163G>A, p.Ala1055Thr) variation was of germline origin.

**Case 2**

A 53-year-old male had a colonoscopy as part of a medical examination program at a local hospital. Multiple colon polyps were observed on colonoscopic examination, and the patient was referred to Jeonbuk National University Hospital for further evaluation. Abdominal computed tomography and colonoscopic evaluation were performed. Abdominal computed tomography scans showed no abnormalities such as mass. Colonoscopy revealed the presence of approximately 20 polyps (Figure 2A). Based on the number of colon polyps, the patient was diagnosed with AAP. The size of the largest polyp was 8 mm. Although no cancer was found, the size of this polyp indicated the need for total colectomy. Macroscopically, multiple polyps were identified; and all polyps were diagnosed as tubular adenoma (Figure 2B and 2C).

We recommended genetic evaluation to the patient, and the patient consented. We performed NGS panel testing with an Oncomine Comprehensive Assay Plus (Thermo Fisher Scientific, Waltham, MA, USA) panel using normal tissue from the patient. The results showed variation in the \textit{MSH6} gene (c.3163G>A, p.Lys1358AspTer). The \textit{APC} gene was unaltered. Since the NGS was performed with normal tissue, the variation in the \textit{MSH6} gene was concluded to be the result of germline variation. The patient had two children on whom NGS of normal tissue was performed and showed the genetic variant inherited from their father.

**Discussion**
Detection of AAP is significantly increasing [1, 2]. The increase of AAP incidence is mostly due to the improvement of imaging and application of screening programs for colorectal cancer detection [1]. AAP is diagnosed when there are more than 10 and less than 100 adenomas in the colon and rectum [2]. AAP patients are a highly heterogenous group regarding severity of disease, family history, and risk for development of CRC. The burden of adenoma can be mild to severe, and risk for development of CRC ranges from 40–80% depending on this burden [2]. Age at diagnosis is variable, but AAP patients are generally older than CAP patients [2]. In contrast to CAP, family history of AAP is not a common finding [2].

Variations in APC and MUTYH genes have been reported to cause CAP [1]. Heterogenous variation of the tumor suppressor gene APC resulting in truncation of the protein is the main cause of CAP, and CAP caused by APC variation shows a dominant inheritance pattern [1]. In addition, bi-allelic variations in the MUTYH gene, which is involved in DNA repair, causes a minority of CAP cases [1]. However, < 20% of AAP cases are caused by variations in the APC and MUTYH genes; the genetic variants that may be responsible for a significant number of AAP cases are unknown [1]. Studies to elucidate the underlying genetic alterations associated with AAP are on-going. With the recent development of sequencing technology, new genetic alterations that cause AAP are being identified [7–10]. Other than APC and MUTYH genetic alterations, variations in POLE, POLD1, NTHL1, MSH3, and MLH3 genes have been reported in AAP cases [1].

In our report, germline variation in the MSH6 gene was detected in both AAP patients. MSH6 functions in DNA mismatch repair (MMR) [11]. The protein product hMSH6 combines with hMSH2, the protein product of the MSH2 gene, and recognizes replication errors in microsatellite sequences [11]. Mutations in MMR genes lead to deficient function in DNA MMR and can cause hereditary non-polyposis colorectal cancer (HNPCC) syndrome (Lynch syndrome) [12]. Although there is a report of MSH6 variation in serrated polyposis, to the best of our knowledge, variations of the MSH6 gene have not been reported in colorectal polyposis syndromes such as CAP and AAP.

MSH3 encodes hMSH3, an alternative hMSH2 binding partner to hMSH6. hMSH2 has to be combined with hMSH3 or hMSH6 in order to exercise its function. In recent reports, two AAP patients were identified to have bi-allelic truncating variations in the MSH3 gene [9]. The clinical significance of the MSH6 mutations detected in our AAP patients is unknown. However, since MSH3 and MSH6 share functions, and mutations in MSH3 were observed in previous AAP patients, deficiencies in MMR may affect the occurrence of AAP as well as the well-known occurrence of HNPCC.

In conclusion, we report two cases of AAP with germline MSH6 variation. Further research is needed to clarify the significance of MSH6 variation in AAP patients.

**Abbreviations**

AP Adenomatous polyposis
Declarations

Acknowledgments

None.

Authors’ contributions

Lee ML and Ha GW provided the interesting cases that we reported. Lee ML and Ha GW performed the surgery and provided treatment for patient. Ahn AR, Kim KM, and Chung MJ analyzed the NGS sequencing data. Kim KM evaluated the histopathological images and prepared the figures. Kim KM and Ha GW write the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and consent to participate

This study followed the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the Jeonbuk National University Hospital with a waiver of informed consent (IRB No. 2023-02-024). The participant’s legal guardian provided signed written informed consent to participate in this study.

Consent for publication

Written informed consent was obtained from the participants’ legal guardian for publication of this case report and any accompanying details and images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests
The authors declare that they have no competing interests.

References


Figures
Figure 1

(A) Endoscopy of the colon revealed multiple polyps. (B) Histologic features of the patient’s colon cancer. Tumor cells are infiltrating the smooth muscle layer (H&E stain, magnification: x100). (C) Low-power view of the colon polyps (H&E stain, magnification: x20). (D) The polyps show tubular glands with dysplasia (H&E stain, magnification: x100).
Figure 2

(A) Colonoscopic evaluation showing multiple polyps. Histologic features of the colon polyps. Low-power view of the colon polyps (H&E stain, magnification: x20). (D) The polyps show tubular glands with dysplasia (H&E stain, magnification: x100).