

## Cancer Genetics Report

# A novel germline *BMPR1A* variant (c.72\_73delGA) in a Japanese family with hereditary mixed polyposis syndrome

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## Abstract

Hereditary mixed polyposis syndrome (HMPS) is a rare autosomal dominant disorder characterized by a mixture of typical and/or atypical juvenile polyps, adenomas and hyperplastic polyps, resulting in an increased risk of colorectal cancer. In HMPS, four different germline *BMPR1A* variants from five unrelated families have been reported. This study is the first to report HMPS within a Japanese family. The proband underwent repeated colonoscopic polypectomies over a 5-year period, since the age of 67. Histological examination of these resected polyps revealed adenomas, juvenile-like polyps and hyperplastic changes. Genetic testing was conducted to identify the causative genes for hereditary gastrointestinal cancer syndromes, including *BMPR1A*. We detected a germline variant, c.72\_73delGA, in *BMPR1A*. The proband's elder brother, younger sister and nephew have also undergone repeated colonoscopic polypectomies at other clinics. His sister and nephew underwent genetic testing, and the same *BMPR1A* variant was identified.

**Key words:** hereditary mixed polyposis syndrome, *BMPR1A*, juvenile polyposis syndrome

## Introduction

Hereditary mixed polyposis syndrome (HMPS) is a rare autosomal dominant disorder. It is characterized by colorectal polyposis consisting of various polyp types, including tubular/villous/tubulovillous adenomas, serrated adenomas, hyperplastic polyps and hamartomatous polyps such as typical and/or atypical juvenile (juvenile-like or juvenile-type) polyps (1–3). In addition, HMPS is known to be associated with an increased risk of colorectal cancer (2,4). Clinical diagnostic criteria for HMPS have yet to be firmly

established, as HMPS is considered to encompass heterogeneous disease entities. Recently, HMPS was divided into two subtypes: HMPS-1 (OMIM #601228) (<https://www.omim.org/entry/601228>), which is associated with germline duplication of *GREM1*, and HMPS-2 (OMIM #610069) (<https://www.omim.org/entry/610069>), which has germline variants in *BMPR1A*. Currently, HMPS-2 has only been reported in four Chinese families and one Irish family (3–5). In this study, we report a novel germline *BMPR1A* variant in a Japanese family with HMPS-2.

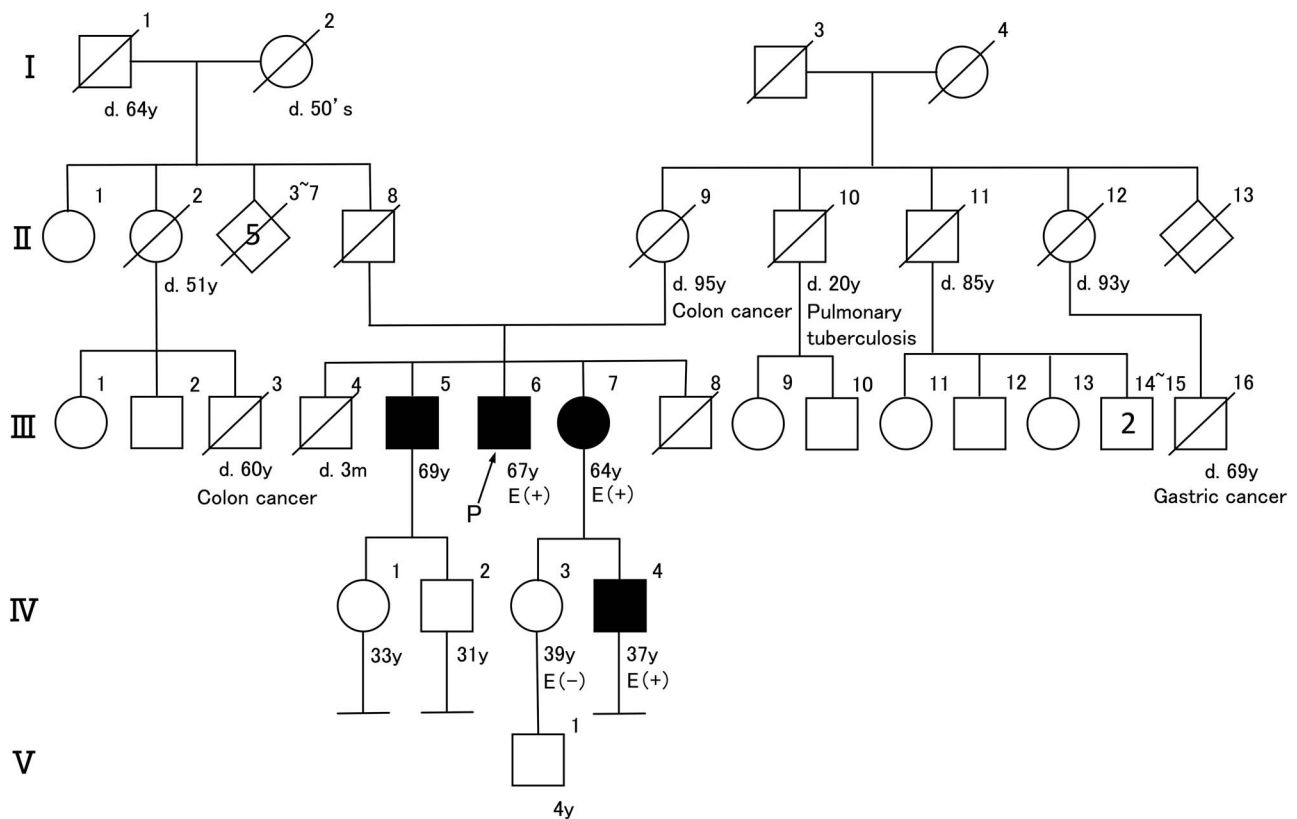


Figure 1. Pedigree of the reported family.

### Case presentation and genetic analysis

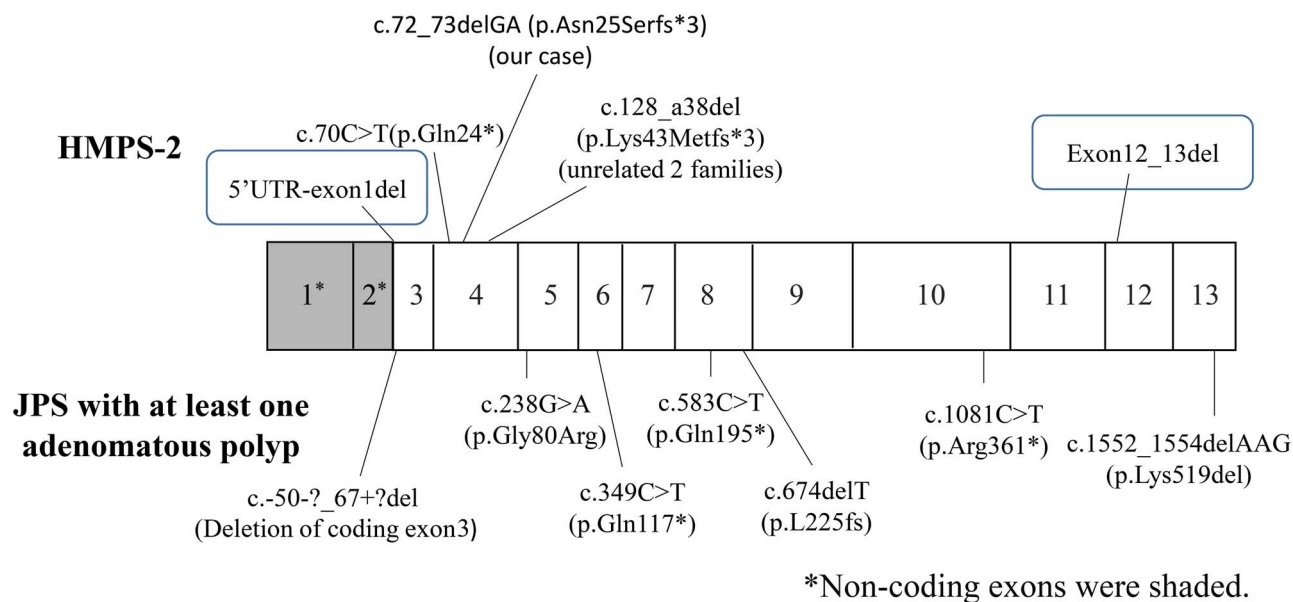
The pedigree tree of this family is shown in Fig. 1. The proband (III-6) was a 67-year-old Japanese man who had undergone a colonoscopy due to occult blood found in a medical check-up. The colonoscopy detected multiple polyps throughout the large intestine, and over the next 5 years a total of 25 colorectal polyps were removed. Histological examination of these polyps revealed six tubular adenomas; 12 juvenile polyps; four atypical juvenile (juvenile-like) polyps, which do not fulfil the findings of typical juvenile polyps (6); two juvenile polyps with coexisting tubular adenoma; and an atypical juvenile polyp with coexisting tubular adenoma (Supplementary Material, Table S1 and Fig. S1). We performed an esophago-gastroduodenal endoscopy, a capsule endoscopy; and a thoracoabdominal pelvic contrast-enhanced computed tomography to screen other organs, but there were no other neoplastic lesions in the proband. The proband's elder brother (III-5), younger sister (III-7) and nephew (IV-4) had multiple colorectal polyps removed in their 50s and 60s (III-5 and III-7) and 20s and 30s (IV-4) at another clinic or hospital. The proband's paternal cousin (III-3) and mother (II-9) died of colon cancer at 60 and 95 years of age, respectively. The presence of colorectal polyps in these two relatives (III-3 and II-9) was unclear. Although pathologic data of the polyps removed from the proband's three relatives (III-5, III-7, and IV-4) were not available, we considered that the family history suggested HMPS. A genetic analysis of a multigene panel analysis of 60 genes originally developed using next-generation sequencing technology for the purpose of diagnosing hereditary colorectal cancer and gastrointestinal polyposis (7) was approved by the local ethics committee of Saitama Medical University (No. 747-VII). After genetic counselling, the proband provided written informed consent

for genetic testing. Genomic DNA was extracted from peripheral blood leukocytes using a standard procedure. A frameshift variant (c.72\_73delGA, p.Asn25Serfs\*3; Chr10:86890066\_86890067del on GRCh38) of *BMPRIA* (NM\_004329.2) was identified by the multigene panel analysis and confirmed by Sanger sequencing (Supplementary Material, Fig. S2).

The proband's younger sister (III-7) underwent genetic testing for the *BMPRIA* variant, leading to a positive result. Her daughter (IV-3) and son (IV-4) also underwent genetic testing for the *BMPRIA* variant. Only her son (IV-4) also carried the same *BMPRIA* variant. The proband's elder brother refused genetic testing. We requested pathologic and endoscopic data of the two relatives (III-7 and IV-4), but their medical records were no longer available, as their last colonoscopic examinations occurred at least 9 years earlier. The treating physician remembered that at least one polyp, >30 mm in diameter, was removed in both patients. Repeat colonoscopies were therefore preformed in their case. The proband's sister (III-7) had one sigmoid polyp removed endoscopically, but no other colorectal polyps were identified. Histological examination of the removed polyp revealed tubular adenoma. The proband's nephew (IV-4) had one sigmoid colon polyp endoscopically removed and had one rectal polyp surgically removed. Histological examination of the endoscopically removed polyp and the surgically removed polyp revealed juvenile-type polyp and traditional serrated polyp, respectively.

### Discussion

Although standard clinical diagnostic criteria for HMPS have yet to be firmly established, HMPS differs from juvenile polyposis



**Figure 2.** Comparison of pathogenic variants of *BMPRI1A* between patients with hereditary mixed polyposis syndrome (HMPS)-2 and those with juvenile polyposis syndrome (JPS) with at least one adenomatous polyp, reported in the literature.

syndrome (JPS) in that only a few typical juvenile polyps are documented. If typical juvenile polyps are present in HMPS, they are often associated with mixed components (3,4). HMPS patients are rarely diagnosed before the third decade of their life. In contrast, JPS affects infants or children between ages 5 and 15 years, often manifesting with 50 or more juvenile polyps (8). The incidence of colorectal cancer associated with JPS is also lower than that of HMPS (9). However, specialized centres have reported the existence of adenomatous components or adenomas in two and 15% of JPS cases (10,11). In addition, germline *BMPRI1A* variants have been shown to be the underlying molecular defect in about 20% of JPS patients (12–14). As characterized in HMPS, juvenile polyp components have been reported to be present in the mixed polyps of some HMPS families (2,4). Thus, it has been proposed that, from the viewpoint of molecular genetics, HMPS (especially HMPS-2) and JPS may be categorized into the same disease entity (2,4). Despite this, it should be noted that JPS and HMPS-2 are clinically defined syndromes. It is possible that different syndromes share the same germline defect and that subsequent interplay of downstream ligands and receptors leads to different biological processes and consequently subtle phenotypical differences.

To the best of our knowledge, there have only been five germline *BMPRI1A* variants from six HMPS-2 families including our reported family. Of these, Cheah et al. (4) reported the same variants from two unrelated families, which were confirmed by microsatellite analysis. Notably, the sites of the variants were located between 5'UTR and exon 4 of *BMPRI1A* in five of six families. Calva-Cerqueira et al. (14) reported no hotspots concerning germline *BMPRI1A* variants in families with JPS. Furthermore, based on the data reported by Calva-Cerqueira and associates (14) and our hand-search of the ClinVar database (<https://www.ncbi.nlm.nih.gov/clinvar/>), we found seven germline *BMPRI1A* variants in JPS patients harbouring at least one colorectal adenoma, whose phenotypes may be useful for considering the molecular (genotypic) difference between JPS and HMPS-2. The sites of variants in these cases,

except for one case, were located at exon 5 or its downstream, which are in contrast with the sites of the cases of HMPS-2 families (Fig. 2). Genotype–phenotype relationships in families with JPS with *BMPRI1A* variants and those with HMPS-2 deserve further investigation to determine whether HMPS-2 is merely a subtype of *BMPRI1A*-associated JPS.

We suspected our reported family as HMPS because of the proband's typical colorectal polyp phenotype and pedigree information consistent with the autosomal dominant inheritance. However, Cheah et al. (4) reported the following: (i) juvenile polyps were not documented in all affected members of the HMPS families and, if reported in some cases, were few in numbers (between one to three polyps). (ii) The difficulty in diagnosis thus lies in distinguishing HMPS from attenuated FAP rather than JPS. Indeed, Singapore HMPS families were often misdiagnosed as FAP and none as JPS. Therefore, multigene panel analysis including genes (*APC*, *MUTYH*, *SMAD4*, *BMPRI1A*, etc.) associated with some polyposis syndromes is mandatory in the diagnosis and differential diagnosis of patients and relatives with HMPS.

### Supplementary material

Supplementary material are available at *Japanese Journal of Clinical Oncology* online.

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### Conflict of interest statement

None declared.

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